Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

MAY--1956
Volume 6 — Number 5

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1. Arnoff, B.: Personal communication. 2. Lazarte, J. A., and Petersen, M. C.: Personal communication.

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1. Seifter, J., et al.: To be published. 2. Fazekas, J.F., et al.: M. Ann. District of Columbia 25:67 (Feb.) 1956. 3. Mitchell, E.H.: J.A.M.A. In press.

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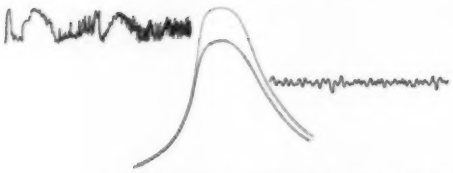

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1. Doyle, P. J., and Livingston, S.: J. Pediat. *43*:413 (Oct.) 1953.
2. Livingston, S., and Petersen, D.: To be published.
3. Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.

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1. Hollister, L. E., Krieger, G. E., Kringel, A., and Roberts, R. H.: Ann. New York Acad. Sc. *61*:92 (April 15) 1955. 2. Hoffman, J. L., and Konchegul, L.: Ann. New York Acad. Sc. *61*:144 (April 15) 1955. 3. Kline, N. S., and Stanley, A. M.: Ann. New York Acad. Sc. *61*:85 (April 15) 1955.

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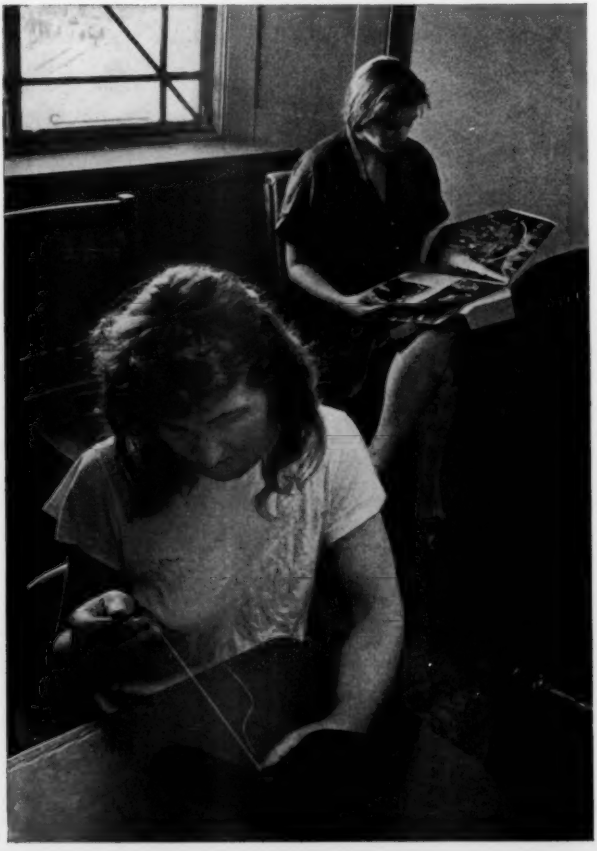

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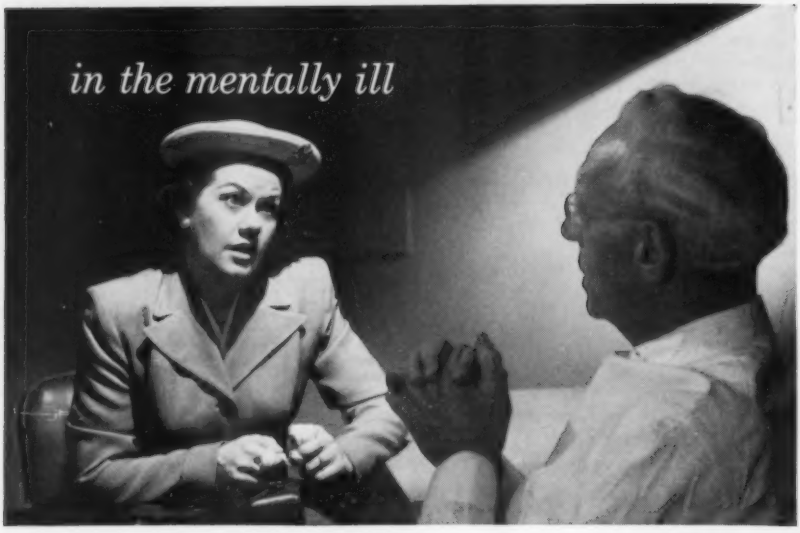

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(1) Rodriguez-Gomez, M.; Valdes-Rodriguez, A., and Drew, A. L.: J.A.M.A. 160:752 (Mar. 3) 1956. (2) Amols, W.: J.A.M.A. 160:742 (Mar. 3) 1956. (3) Abrahamsen, E. H., and Baird, H. W., III: J.A.M.A. 160:749 (Mar. 3) 1956. (4) Smith, R. T.; Kron, K. N.; Peak, W. F., and Hermann, I. F.: J.A.M.A. 160:745 (Mar. 3) 1956.

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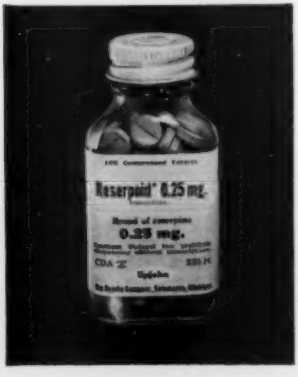

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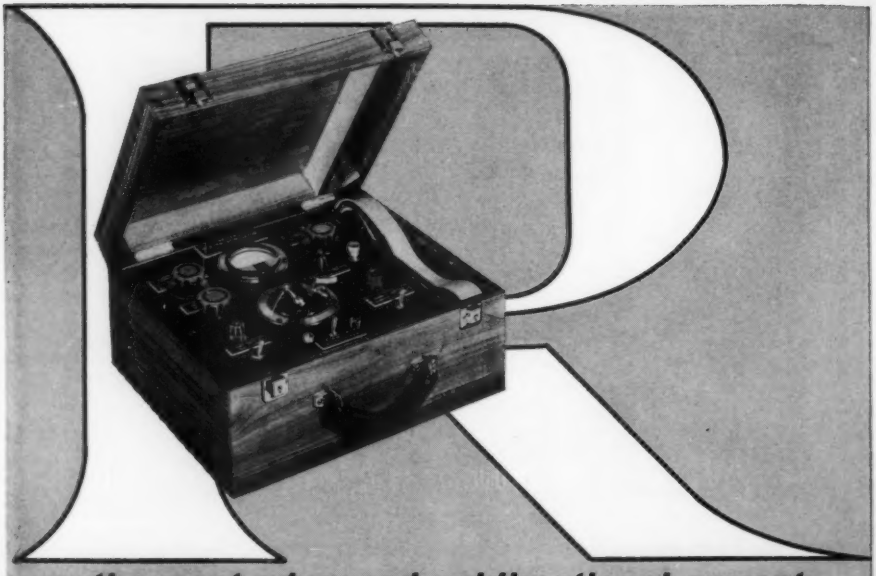

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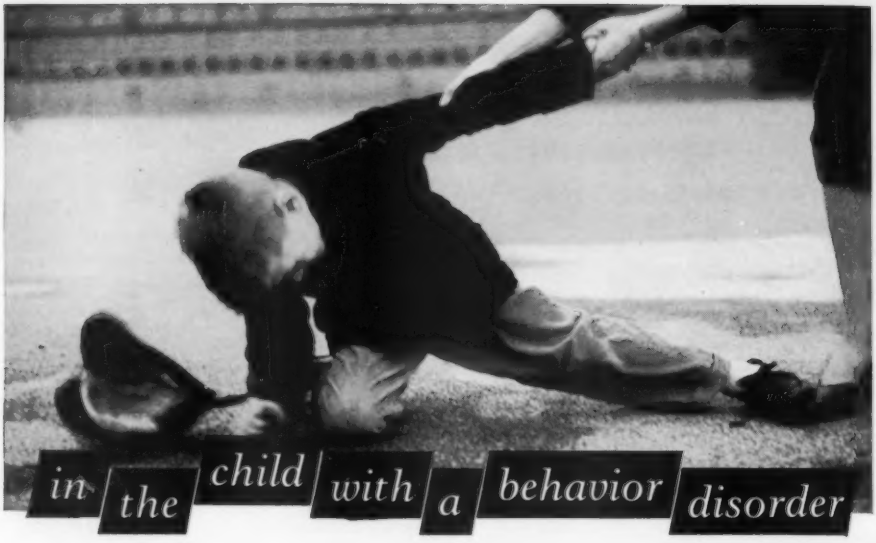

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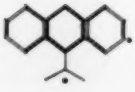

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Volume 6 Neurology Number 5

Fatalities in Myasthenia Gravis

A Review of 39 Cases with 26 Autopsies

Lewis P. Rowland, M.D., Paul F. A. Hoefer, M.D., Henry Aranow, Jr., M.D. and H. Houston Merritt, M.D.

THE MORTALITY RATE of myasthenia gravis is high, despite the advances in therapy of the past two decades. We have reviewed the records of patients with myasthenia who died at the Columbia-Presbyterian Medical Center, in order to evaluate factors which might be responsible for these fatalities and to describe the clinical and pathologic features of a group of patients in whom the disease has been followed to its end.

CASE MATERIAL

During the period from 1930 to 1955 the diagnosis of myasthenia gravis was established unequivocally in 180 patients,[74] all but 13 of whom were seen after 1940 (figure 1). Fifty-five patients are known to have died, a mortality rate of at least 30 per cent. The actual figure is uncertain, since 49 patients have not been followed.

Thirty-nine fatal cases have been selected for review and are the subject of this report, including all of the 34 patients who died in the hospital, two patients who were dead upon arrival at the hospital, two patients who died at home while under our care, and one patient who died at another hospital but who had been seen on our service initially and whose postmortem examination was performed in our department of pathology; other patients who died elsewhere have been excluded. Knowledge of the terminal events was available for each of the cases included and postmortem examination was performed in 26 cases. Only three patients died prior to 1940 (figure 1).

CLINICAL ANALYSIS — GENERAL FEATURES

Age and sex incidence. Of the 39 patients, 13 were men and 26 were women

From the departments of neurology and medicine, College of Physicians and Surgeons and The Presbyterian Hospital, New York City.

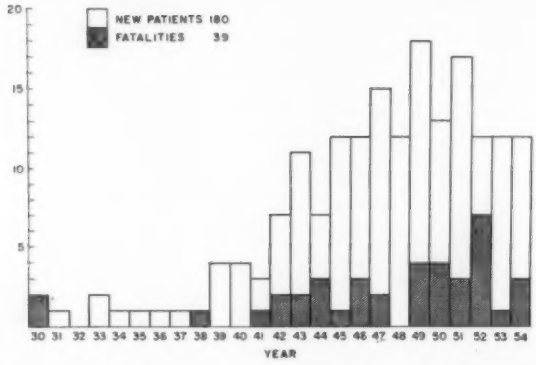

FIG. 1. The number of new patients with myasthenia gravis seen each year at the Columbia-Presbyterian Medical Center and the annual distribution of the fatal cases described in this report.

(table 1). Of the 26 women, 16 (62 per cent) noted the onset of symptoms before the age of 40 and 13 (50 per cent) died before this age. In contrast, only two of the 13 men (15 per cent) had symptoms prior to the age of 40 and only one died before this age. There were no patients under the age of ten, but there were five whose disease started after the age of 60.

Duration of symptoms. The duration of continuous symptoms (table 1) varied from two weeks to 12 years (mean 2.8 years). None of the male patients had continuous symptoms for more than five years, although two had ocular symptoms alone for a few months, followed by remissions of six and 20 years respectively, prior to the onset of persistent and generalized symptoms. Among the women, however, seven (27 per cent) had symptoms for more than five years. On the other hand, six (23 per cent) of the women had symptoms for less than six months and 15 of all fatal cases (38 per cent) succumbed within one year of the onset. It has been suggested that myasthenia gravis is especially malignant in young women,[174] but the most fulminating cases in the present series occurred in older age groups; some patients died within six months after onset

TABLE 1
DISTRIBUTION OF 39 FATAL CASES OF MYASTHENIA GRAVIS ACCORDING TO AGE AT ONSET, SEX, AND DURATION OF SYMPTOMS
Number of Patients

Age at onset	*Less than 6 months*	*6 months to 1 year*	*1 to 2 years*	*2 to 5 years*	*More than 5 years*	*Male*	*Female*	*Total*
10 to 19	0	1	2	2	1	0	6	6
20 to 29	0	0	1	0	3	1	3	4
30 to 39	2	1	0	3	2	1	7	8
40 to 49	1	2	0	4	1	4	4	8
50 to 59	3	1	2	0	2	4	4	8
60 to 69	2	1	0	0	0	2	1	3
70 to 79	0	1	1	0	0	1	1	2
								39
Male	2	4	3	2	2			13
Female	6	3	3	7	7			26
								39

in each decade between 30 and 70 years.

Remissions. Six patients enjoyed complete remissions of symptoms without need for medication during the remission. Two patients had two separate remissions and one also had a partial remission later. The other three had only single remissions. Four of these eight complete remissions occurred within one year of the onset of symptoms, but one occurred after six and a half years of illness. The periods of remission varied from one month to 20 years; three lasted five years or more.

Three other patients had partial remissions during which there was a marked diminution in the severity of symptoms and notable decrease in neostigmine requirements. Three of the four partial remissions occurred within the first 18 months of illness and none exceeded six months in duration.

Nonfatal respiratory crises. Six patients survived episodes of respiratory failure requiring the use of a mechanical respirator before succumbing in a subsequent similar attack. In five of the six, the first crisis occurred within six months of death; one patient lived for 14 months after respirator treatment.

Precritical symptoms. All but one of the 39 patients had severe generalized myasthenia by the time they died. The exception was a patient whose death was related to surgery and who had no previous history of respiratory difficulty. All others had dyspnea, dysphagia, dysarthria, ocular symptoms, and weakness of the extremities, although the nature and severity of symptoms at the onset varied from patient to patient.

COMPLICATING FEATURES

In 16 patients there was no history of associated illness which could have been a factor contributing to the terminal crisis.

TABLE 2

INCIDENCE OF COMPLICATING FEATURES IN 39 FATAL CASES OF MYASTHENIA GRAVIS

	Number of Patients
Conditions possibly fatal of themselves:	
Thyrotoxicosis	2
Post-thymectomy	2
Convulsive disorder of unknown etiology (acute)	1
Pernicious anemia	1
Fulminating pneumonia	1
Luetic aortitis	1
Myocarditis	2
Cerebral contusions	1
*Conditions usually not fatal:**	
Pregnancy	2
Respiratory infection	10
Pneumonia	6
Diabetes, mild	2
Syphilis, asymptomatic	2
Convulsive disorder of unknown etiology (chronic)	1
Hypertensive vascular disease (mild)	3

*Some patients had more than one of these conditions.

Major concurrent diseases. Ten of the 39 patients had complicating conditions in addition to myasthenia gravis which might have played an independent role in causing death (table 2). In individual cases it is difficult to determine whether the complicating condition or the myasthenia was more important in causing death, but in every patient muscle weakness was prominent.

Two patients had both myasthenia and thyrotoxicosis at the time of death. In each case the course was progressively downhill once both syndromes appeared, and there was no improvement of one syndrome as the other became worse. Medical therapy, including neostigmine, propylthiouracil, and respirator care, was ineffective.

One patient who died two hours after admission to the hospital had fulminating pneumococcal pneumonia, and one patient died of respiratory paralysis and shock four days after a fall which resulted in multiple cerebral contusions and subdural hemorrhage.

One patient who died suddenly and unexpectedly had a syphilitic aneurysm of the aorta. She had previously experienced episodes of respiratory obstruction due, in part, to lingual weakness. At autopsy there was no evidence of aortic valvular insufficiency, rupture of the aneurysm, or encroachment upon coronary ostia so that myasthenia was the presumptive cause of death.

Myasthenia also seemed to be largely responsible for the death of three other patients who had complicating diseases but in whom postmortem examination was not obtained. One had a macrocytic anemia, congestive heart failure, and an organic mental syndrome. One had convulsions of unknown etiology. The third had episodes presumed to be pulmonary edema.

Two patients died after thymectomy, one of cardiac arrest when the skin was being closed after an uncomplicated operative procedure, and the other in a respirator two days after surgery following a stormy postoperative course complicated by pneumothorax.

In two other cases an unsuspected myocarditis was found at autopsy. One of them had severe orthopnea and tachypnea and was also found to have a pulmonary embolus at necropsy.

Other complicating conditions. Ten patients had symptoms of upper respiratory infection immediately prior to the terminal crisis and six of the ten also had clinical evidence of pneumonia at the time of admission.

One patient was in the third month of pregnancy at the time of death, and another had delivered a normal child three weeks before she died. In both cases myasthenia started at the beginning of pregnancy and in neither case did remission occur.

Eight patients had disorders presumably not contributory to death: diabetes mellitus (two cases), asymptomatic syphilis (two cases), mild arterial hypertension (three cases), and a convulsive disorder of long duration and unknown etiology (one case).

Complications related to medication. Two patients died prior to the introduction of neostigmine in the 1930's. All others received neostigmine during the course of the illness and most of them during its final stage. Some, in addition, were treated with other drugs. The influence of dosage of neostigmine and of long-acting anticholinesterases, the effect of withdrawal of medication for various reasons, and the role of sedatives will be analyzed.

In two patients neostigmine medication was discontinued after an initially favorable response to the drug. In one of these cases the diagnosis of myasthenia was questioned; in the other, the patient seemed to have become refractory to 500 mg. by mouth daily. Neither of these two had severe respiratory symptoms at the time of withdrawal. They developed respiratory weakness in 24 and 72 hours respectively and died. In nine patients neostigmine was discontinued when they were placed in a respirator in a crisis.

Eight patients died while receiving experimental drugs. One woman received an analogue of physostigmine for several days and had episodes of what appeared to be pulmonary edema.

Whether this was related to the drug is uncertain, since the clinical picture was not clear, necropsy was not obtained, and similar symptoms did not occur in other patients who received this preparation. Pulmonary edema due to an idiosyncratic reaction to neostigmine has been reported,[104] but it has also been present at autopsy of some cases prior to the introduction of neostigmine.[6,94,144,193]

Another patient was already in a mechanical respirator when di-isopropylfluorophosphate (DFP) was administered in an unsuccessful attempt to reverse his downhill course. One patient was receiving octamethyl pyrophosphoramide (OMPA), 36 mg. daily, and three others were taking 24 to 26 mg. daily; each received supplemental neostigmine and atropine. One patient was receiving pyridostigmine and another W341*. Three of these patients had some diarrhea in the days preceding exitus, but there was no other evidence of drug toxicity.

Fourteen patients received sedative drugs shortly before death; only seven of these were in a respirator at the time. Administration of usually soporific doses to six of those not in a respirator was followed by the onset of coma within 30 to 60 minutes. Four died shortly after coma supervened and the others survived only briefly after being placed in a respirator.

Two patients were receiving placebo medication at the time of death. In each of them saline administered subcutaneously had been followed by improvement of dyspneic attacks; emotional factors were therefore thought to be preponderant. An inert tablet was substituted for neostigmine for three days before death in one, while the other continued to receive neostigmine parenterally alternating with saline. Attacks similar to those which had responded to saline subsequently proved fatal.

*An analogue of neostigmine.

DEATH IN MYASTHENIA GRAVIS PATIENTS NOT IN A MECHANICAL RESPIRATOR

Sudden and unexpected death. Thirteen patients who seemed to be making satisfactory progress died unexpectedly in acute myasthenic attacks which started abruptly and proved fatal within a few minutes or, at most, an hour. In such an attack the patient, previously comfortable, suddenly became obtunded, dyspneic, and cyanotic. Respiratory paralysis, sometimes with lingual or pharyngeal weakness, seemed to be prominent, but the exitus of seven patients was not actually observed.

Three of the latter died in the hospital, illustrating the rapidity of onset and progression of some fatal attacks. Each had been admitted during an acute exacerbation of myasthenia but seemed to be improving. They were all seen a few minutes prior to death and did not seem to be in distress. When next seen a few moments later they were dead. One of these patients was receiving OMPA and had a tracheotomy tube in place for several days. At autopsy the tube was patent and the possibility of sudden blockade of the airway seems to have been excluded. She did, however, have lobular pneumonia with a considerable accumulation of mucus in the bronchi.

Two other patients died abruptly while on OMPA therapy, as did the single patients taking pyridostigmine and W341.

Four of the remaining six patients who died during acute episodes had had one or more serious attacks of respiratory paralysis during the days preceding exitus. The premonitory attacks were usually relieved promptly by the administration of supplemental neostigmine parenterally, and between critical periods their condition seemed satisfactory. The other patient was recovering from an exacerbation of myasthenia accompanied by pneumonia when an acute attack of dyspnea terminated fatally within a few moments.

Age, sex, and duration of symptoms offered no prognostic guide as to the occurrence of sudden death of this nature, nor did the apparent severity of the disease. Pre-admission neostigmine requirements varied from two patients who were doing well on 30 and 45 mg. daily to one who had prominent symptoms but no dyspnea despite 500 mg. daily. Three patients were controlled suboptimally despite substantial amounts of OMPA supplemented by 100 to 300 mg. neostigmine daily by mouth. One patient, a woman whose symptoms lasted only one month, was considered to have a mild form of the disease. One day, however, she suddenly became apneic and lost consciousness. She recovered from this episode but died in similar circumstances a few days later.

Others. There were nine patients who were not in a respirator at the time of death, but in whom a fatal termination was not unexpected and did not occur suddenly. In five of them the appearance of coma or cyanosis was abrupt, but they differed from the patients previously described in that they were already seriously ill at the time of this change, or else the final episode lasted longer than one hour. In four of the five in whom this change was sudden, barbiturates or opiates had been administered within an hour of the change; each had had some respiratory difficulty previously.

Two of the nine patients died prior to the introduction of neostigmine. One died of fulminating pneumonia within two hours of admission. None of the others received large doses of neostigmine after admission, the maximum being 18 mg. parenterally in 24 hours. One patient received only 6 mg. parenterally in 48 hours, although she was known to have bronchopneumonia and had a period of overt dyspnea lasting about 12 hours. Another patient had numerous episodes of respiratory difficulty but received only 300 mg. of neostigmine orally each day.

PATIENTS IN A MECHANICAL RESPIRATOR

Sixteen patients were in a mechanical respirator at the time of death. All but two were cyanotic, comatose, or apneic before they were placed in the respirator. Another indication that respirator treatment was often an emergency measure is the fact that only six patients had a tracheotomy prior to the institution of respirator therapy, while an endotracheal tube was used in nine.

In eight patients the critical change was sudden; at least four patients had repeated premonitory episodes of dyspnea. The respirator was used on the day of admission for four patients and in eight it was used by the fourth day.

The average survival in the respirator was four days. Three patients died within a few hours; only two survived for more than one week.

The management of all respirator patients was essentially the same: constant

TABLE 3

HISTOLOGY OF THYMUS GLAND IN 39 FATAL CASES OF MYASTHENIA GRAVIS

	Number of Patients
Histology of thymus	
Thymoma	11
Thymoma and hyperplasia	1
Hyperplasia	7
Normal	3
Thymic tissue not found at autopsy	8
Not known (patients who had neither roentgenographic evidence of tumor nor histological examination of thymus)	9
Total	39

TABLE 4

BASIS FOR DIAGNOSIS OF THYMOMA IN 12 FATAL CASES OF MYASTHENIA GRAVIS

		Number of Patients
Roentgenographic evidence of tumor present		6
Confirmed by necropsy	1	
Confirmed by surgery	3	
Unconfirmed	2	
Roentgenographic evidence of tumor absent		6
Thymoma at necropsy	5	
Thymoma at surgery	1	
Total		12

nursing care, antibiotics, tracheal suction, and electrolyte maintenance. Seven patients continued to receive neostigmine while in the respirator and nine did not. Of the latter, six patients had serious complicating diseases.

Three respirator patients had significant degrees of carbon dioxide retention and all those examined at autopsy had pneumonitis, pulmonary congestion, or pulmonary edema; five also had atelectasis. The sudden and inexplicable exitus of two patients, however, may indicate that pulmonary complications do not account for all respirator deaths. One woman had been in the respirator for 18 days and her course was stable. One night she was able to take her own temperature and five minutes later seemed to be sleeping comfortably, but when examined a few minutes later she had expired. The other patient was alert and talking when she died suddenly while tracheal suction was being applied. In some of the other patients the degree of pulmonary pathology seemed insufficient to have been lethal.

PATHOLOGY

THYMUS

At autopsy six patients were found to have thymomas (tables 4 and 5) and three others in the autopsy group had thymomas removed surgically, so that nine of the 26 patients in whom postmortem examination was performed had thymomas (35 per cent). In addition, three patients who did not have necropsies had roentgenographic evidence of anterior mediastinal masses thought to be thymomas. One of these was proved by surgery, so that at least 12 of the 39 patients (30 per cent) in the entire series had thymic tumors.

A radiologic diagnosis of thymoma was confirmed histologically four times; there were no falsely positive x-ray diagnoses. On the other hand, five thymomas found at autopsy and one found at operation had not been detected by roentgenographic examination.

Nine of the ten histologically verified tumors were available for review. They all presented the usually described appearance of thymoma.[19,28,112] They varied in size but did not occupy the entire gland and they were all encapsulated. Cyst formation and hemorrhage occurred in one. Microscopically the tumor tissue did not retain the characteristic structure of normal thymus. The tumor cells were fairly uniform in distribution and consisted of two types, one resembling a lymphocyte and the other an epithelial or reticulum cell. Either might predominate in a given tumor, but both cell types were invar-

TABLE 5
CORRELATION OF THYMUS HISTOLOGY WITH AGE, DURATION, AND MODE OF DEATH AMONG 25 FATAL CASES OF MYASTHENIA GRAVIS*

Histology	Number of cases	Duration (months) Range	Duration (months) Average	Age (years) Range	Age (years) Average	Mode of Death Sudden	Mode of Death Respirator	Mode of Death Subacute
Thymoma	10	1.5 to 128	34	31 to 61	50	5	3	2
Hyperplasia	7	1.5 to 128	24	17 to 54	38	3	2	2
Thymus absent	8	0.5 to 144	29	14 to 77	50	1	5	2

*This excludes the two patients who had only roentgenographic evidence of thymoma, without histologic confirmation, and the three patients reported to have normal thymus histology.

iably present. Mitotic figures and Hassall's corpuscles were rare. Fibrous tissue septa were prominent in all, giving the tumor a lobulated appearance. None of the tumors showed histologic evidence of malignancy and there was no evidence of local invasiveness or distant spread.

One exception to this description was the tumor of a patient whose gland contained a local area of hyperplasia, regarded as a thymoma because of its focal nature and the presence of a well-defined capsule. Difficulty in classifying thymic lesions of this type has been noted by others.[22,113] One of the patients whose thymoma had been removed surgically showed hyperplasia of thymic remnants.

Of the remaining cases in which postmortem examination was performed, five showed thymic hyperplasia and one contained a microscopic remnant of normal tissue. In eight cases there was no evidence at all of thymic tissue. Sections of three early autopsies were not available for review; one had been described as hyperplastic, the others as normal.

Because of the variability in size and weight of the thymus, it has been suggested that the concept of thymic hyperplasia should be discarded.[19,28,44] The process diagnosed as hyperplasia in this series involved the entire gland; there was no capsule and histologically the tissue resembled normal thymus, except that cellular elements were present in numbers exceeding that which might be expected for the patient's age. It is recognized that this is a subjective and somewhat arbitrary way of deciding which specimen is normal and which is hyperplastic, but difficulty has also been encountered by those who have attempted to establish more precise criteria.[22]

The presence of germinal centers in non-neoplastic thymus[19,28,132,155] was not prominent in the present series. Five of the eight non-neoplastic glands reviewed contained no such formations and a sixth contained only one suggestive group. The other two contained structures of this nature, but in neither were they so prominent as those illustrated by Castleman and Norris.[28]

MUSCLE

Lymphorrhages in skeletal muscle were found in 16 of the patients in whom postmortem examination was performed. Many of these were perivascular, but in others this distribution was not apparent. The number and extent of these lymphocytic collections varied from patient to patient and from muscle to muscle in the same patient. Only one or two sections were examined in most of the patients in whom no lymphorrhages were found, but in one case ten muscles were reviewed and no lesions were found.

In addition to lymphocytes, plasma

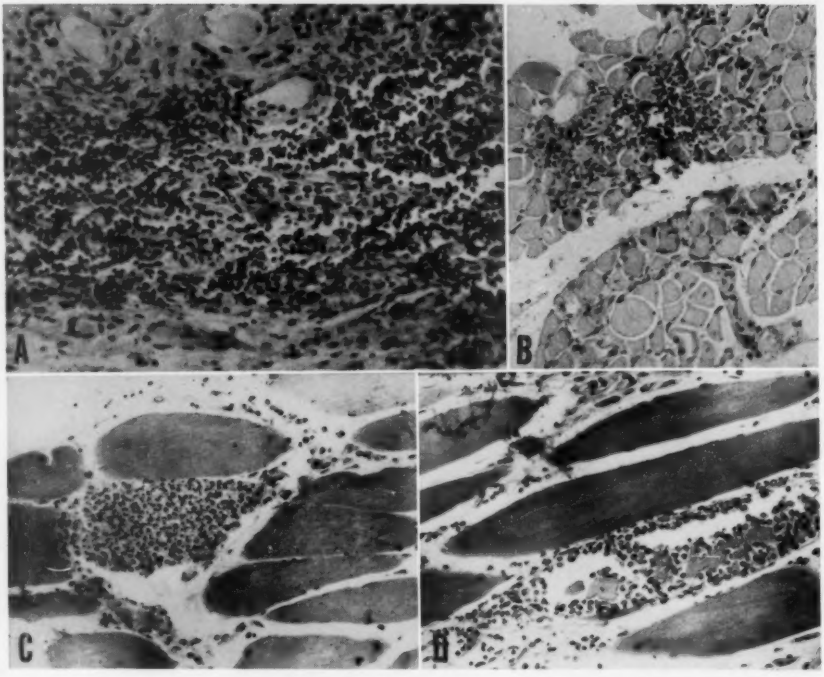

FIG. 2. Lesions of skeletal muscle from three different patients with myasthenia gravis (*C* and *D* are from the same patient). *A*. Diffuse monocytic infiltration among necrotic fibers. *B*. Focal collection of mononuclear cells within and between necrotic fibers. *C*. Focal inflammatory response containing plasma cells, polymorphonuclear cells, and eosinophiles. *D*. Monocytic infiltration of necrotic muscle fiber.

cells were seen occasionally and in one case giant cells and eosinophiles were identified. Polymorphonuclear cells were also encountered in one patient.

Abnormalities of muscle fibers were found in 12 patients, in some of them associated with lymphorrhages. Some shrunken or swollen fibers or focal loss of striation were found in these cases, but the significance of these local changes is uncertain. In three cases, however, definite evidence of muscle necrosis was observed, and in each of these there was pronounced leukocytic infiltration about the degenerating fibers (figure 2).

HEART

Two instances of frank myocarditis were found. In one patient* there was widespread focal degeneration of myocardial fibers, with the formation of granulomatous lesions containing mononuclear cells, polymorphonuclears, eosinophiles, and multinucleated giant cells (figure 3). Eosinophiles and giant cells

*The case history of this patient is described in detail elsewhere.[104]

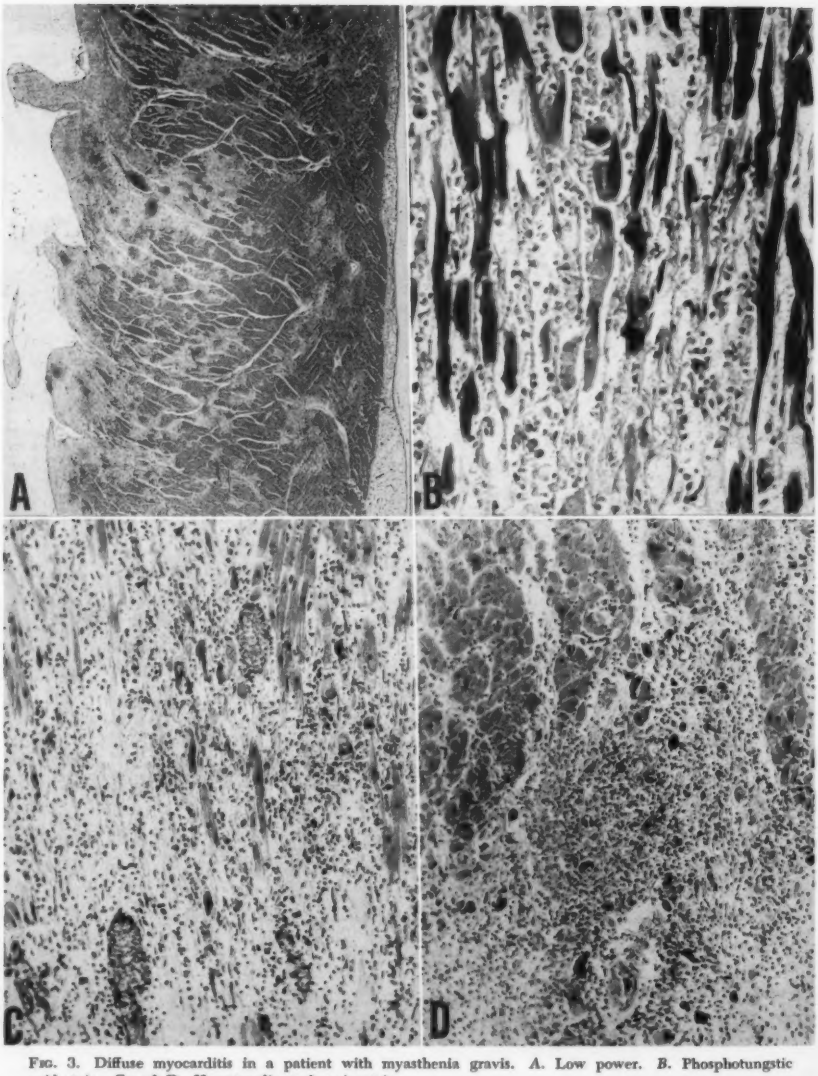

FIG. 3. Diffuse myocarditis in a patient with myasthenia gravis. *A*. Low power. *B*. Phosphotungstic acid stain. *C* and *D*. Hematoxylin and eosin stain.

were also encountered in the skeletal muscles (figure 2C and D). In the other case the myocardial lesions were similar but less intense (figure 4), and only focal lymphorrhages were found in the skeletal muscles. A third patient had

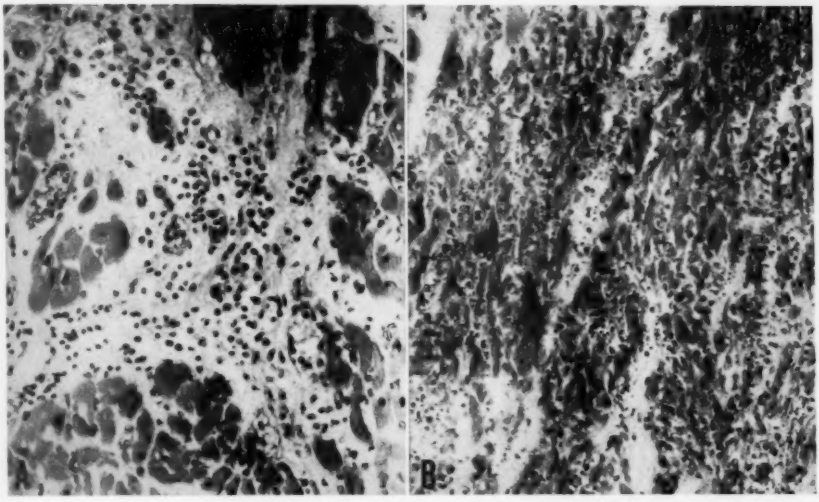

FIG. 4. *A*, Focal, and *B*, diffuse myocardial lesions in another patient with myasthenia gravis.

a small focus of acute myocarditis.

Three other patients had rare accumulations of lymphocytes in the myocardium and in another patient there was some edema of the myocardium. One patient had evidence of healed rheumatic valvulitis, several had coronary arteriosclerosis, and one had a recent coronary thrombosis.

LUNGS

Of the 25 patients whose lungs were examined, 21 had unequivocal pulmonary pathology. The four patients without significant pulmonary findings did not die in the respirator, and two of them died suddenly.

Fifteen patients had pneumonitis, 12 pulmonary congestion, nine pulmonary edema, six atelectasis, and two hydrothorax. Almost all had evidence of bronchial inflammation with accumulation of mucus.

NERVOUS SYSTEM

Peripheral nerves and the central nervous system were examined in 24 patients. In one patient previously reported by McKendree and Wolf,[100] there were changes thought to be possibly related to a previous encephalitic infection. In addition to cerebral contusions due to trauma in one case, the only other lesions were an asymptomatic angioma of the caudate nucleus in one case, asymptomatic cerebral atrophy in another, and congestion of the blood vessels in a few. The brain was not available in either of the two patients who had convulsive disorders.

THYROID

Toxic goiter was found in the single patient who had clinical evidence of thyrotoxicosis and was examined post mortem. In addition, four patients had nontoxic nodular goiters without clinical

evidence of thyroid disease. Lymphocytic infiltration of the thyroid was present in seven patients.

OTHER VISCERA AND ENDOCRINE ORGANS

Visceral congestion was encountered in nine patients, four of whom died in the respirator. Mild fatty degeneration of the liver was found in four cases. One diabetic patient had adenomas of the pancreas, liver, thyroid, and kidney. Two patients had adenomas of the adrenal cortex and another had an adenoma of the liver. Three of the patients with adenomas of other organs also had thymomas. No other significant adrenal lesions were found, and there were no abnormalities in the 22 pituitary glands examined other than lymphocytic infiltration in one case. The eosinophilic accumulations described by Torda and Wolff[168] were not seen.

DISCUSSION

The striking increase in the incidence of the disease in our clinic since 1940 is similar to that in other clinics.[62,163,175] This is probably due to increased interest and better methods of diagnosis rather than a true increase in incidence.

The predominance of women is similar to that of larger series of patients[28, 62,70,74,84,170,179] although equal sex incidence has been reported by some. The distribution of adult patients by age at onset is not strikingly different either, except for the absence of men under the age of 40. The number of women whose disease started before 40 (61 per cent) is similar to that reported by others.[70,148]

The incidence of remission (23 per cent) in the present series is only slightly less than that reported by Kennedy and Moersch,[82] Harvey,[70] and Grob.[62] These authors have also noted that remissions tend to appear early, but in each group there have been some remissions long after the onset of symptoms.

The over-all mortality rate in the present series (over 30 per cent) is comparable to the figures given by Grob and Harvey (32 per cent)[65] and Mathisen (39 per cent).[96]

Fifty-four per cent of our fatal cases died within two years of onset of symptoms. This represents about 12 per cent of our total series of 180 patients. This is identical to the corresponding figures reported by Eaton and co-workers.[45]

The average survival from the onset of symptoms in our fatal group was 2.8 years. Of the 60 cases collected by Campbell and Bramwell in 1900,[27] 23 (38 per cent) died after an average illness of 1.5 years. The similarity of these figures might be interpreted to indicate that now, as then, a large percentage of patients die early in this illness, perhaps due to a malignant form of the disease, and that modern therapy has not succeeded in prolonging life significantly for this group.

SIGNIFICANCE OF CERTAIN COMPLICATIONS

Respiratory infection. The most frequent illness precipitating the final crisis was upper respiratory infection, which seems to induce an aggravation of general weakness by some unexplained mechanism. Additional dysphagia and difficulty in coughing may lead to pneumonitis, inspissation of mucus, atelectasis, and pulmonary edema. The significance of this is emphasized by the fact that all but four of the patients examined post mortem had some degree of pulmonary pathology. It is apparent

that the methods employed to prevent these complications have been inadequate.

The fact that almost all of the patients who died in a respirator suffered severe anoxia prior to the institution of respirator therapy may have contributed to the pulmonary pathology[40] and to the fatal outcome. However, four of 17 patients who recovered from similar respiratory crises on our service also suffered degrees of hypoxia sufficient to produce unconsciousness.[75]

Thyrotoxicosis. The presence of hyperthyroidism in two of the 39 patients is similar to the incidence of thyrotoxicosis among myasthenics reported by others[9,62,75,111] In each of these series, 4 to 5 per cent of the patients with myasthenia have also had thyrotoxicosis, a figure which is probably outside the range of chance. Additional evidence of some relation between these syndromes is suggested by reports of lymphorrhages[41] and hyperplasia of the thymus[98] in hyperthyroidism.

It has been said that there is an inverse or "see-saw" relation between the two disorders. Cases are cited in which myasthenic symptoms increased or appeared for the first time after the hyperthyroidism was treated,[16,33,93,99,166,231] and some patients with both disorders have died after thyroidectomy.[9,33,67,99] There is, however, no definite pattern of association. The diseases may appear concomitantly, or either may precede the other.[67,91,111] Often the thyrotoxicosis has been treated successfully and the patients were euthyroid many years before myasthenia appeared. In some cases thyroidectomy alone[11,120,165,179] or thyroidectomy and thymectomy together[9] have been followed by amelioration of myasthenia as well as hyperthyroidism.

Millikan and Haines[111] emphasize the fact that when both diseases occur simultaneously the outlook may be grave.

Pregnancy. The influence of pregnancy upon myasthenic symptoms has also been extremely variable. Viets, Schwab, and Brazier[176] reported that the most frequent pattern is a slight worsening early in pregnancy, followed by a remission and then a return of weakness in the postpartum period. Keynes[84] noted remission in ten of 17 patients during pregnancy, and others have been impressed by the frequency of remission in pregnant women. The onset of myasthenia during pregnancy, however, or in the postpartum period has been described many times.[47,49,58,65,82,167,179] Furthermore, in seven of Keynes' cases and in all of the 12 pregnancies reported by Kennedy and Moersch, there was either no change or an aggravation of myasthenia. Others have reported exacerbation of myasthenia,[49,65,68,74] and some patients have died.[23,86,128,167] When more than one pregnancy occurs in the same woman, the effect of each on the myasthenia may be different.[4,15,49,89] Finally, therapeutic abortion has been followed by both improvement[53,89,182,191] and aggravation of myasthenia.[65,86,107]

Some early authors[36,53,177,182] recommended therapeutic abortion, but recently it has been contended that this is almost never indicated.[58,84,176] The two patients reported here are the first fatalities related to pregnancy to be recorded since 1936, and the variable course of the disease precludes any definite statement about the management of pregnancy in myasthenic women.

Thymoma. Ever since the first description of a thymoma in a myasthenic patient by Weigert in 1901[183] and the report of Bell in 1917,[13] discussion has centered about the thymus and its possible relation to the pathogenesis of the syndrome. The following observations have been marshalled to suggest that the thymus elaborates some curare-like substance: the frequent association of myasthenia with thymic abnormalities,[28, 76,108] the striking improvement of many patients after thymectomy,[44,70,85,134] and the demonstration of blocking substances in thymic extracts of myasthenic patients.[2,34,150,186,187,188]

If this hypothesis is correct, however, it does not account for all cases. Thymic abnormality is not invariably present, and in the present series complete absence of discernible thymus occurred in almost one-third of autopsied cases. Thymectomy is unsuccessful in many patients. Improvement after thymectomy may be delayed for several months and may be followed by fatal relapse without anatomic evidence of recurrence. There is no correlation between size or cellularity of the thymus and severity of symptoms.[51] Many attempts to repeat the demonstration of a curare-like product from the thymus have been unsuccessful.[14,17,98,140,151]

The incidence of thymoma among autopsied cases in the present series (35 per cent) is about the same as the 30 per cent of 330 cases collected from the literature up to 1949 by Castleman and Norris.[28] Eaton and co-workers[45] state that the true incidence of thymoma more closely approximates 15 per cent. One reason for this discrepancy may be that the group under consideration is composed solely of fatal cases; the incidence of thymoma may be significantly lower in surviving patients. It is said that patients with thymoma have a more rapid course[28] and do less well after thymectomy[45,85,113] than patients who have no tumor, but we are unable to demonstrate any significant difference in the duration of symptoms of patients in our series who had thymomas and those who did not (table 5).

Three patients provide striking illustrations of the variable course of patients with thymoma. The tumor of one patient was demonstrated radiologically 20 years prior to his death, but he was free of symptoms almost all of that time. Two other thymomas were discovered when the patients had no symptoms other than cough. Thymectomy was performed immediately in one case and two years later in the other. The first patient was asymptomatic for five years after thymectomy and then developed myasthenic symptoms, while myasthenia appeared in the other patient a few weeks after thymectomy. Hyperplastic thymic remnants were discovered at autopsy in the second case, but postmortem examination was not obtained in the first patient, so that neither recurrence of the tumor nor the presence of a second tumor in an atypical location[97] can be excluded. Two other cases have been reported[48,103] in which there was a latent interval between thymectomy and the appearance of myasthenic symptoms, but in both invasiveness of the tumor precluded complete removal.

All but one of the thymomas in the present series were found in patients over 40, substantiating reports that these tumors are unlikely to occur in young patients.[28] The patients in whom no thymic tissue was found were also all over 40. Absence of thymic tissue has not been a common feature of the re-

ports of patients subjected to thymectomy. On the other hand, hyperplasia was found in younger patients. Although this may be related to the subjective decision of the pathologist as to normality or hyperplasia for an age group in which the gland is likely to be present, only two of the eight patients with thymic hyperplasia were under 20 and three patients were over 50.

The benign nature of all tumors in this series is consistent with the general experience. Although malignant tumors associated with myasthenia have been recorded, it is noteworthy that malignancy has been denoted by local invasiveness[19,80,90,109,122,129] or pleural implantation.[39,119] Only a few have spread beyond the thoracic cavity and these have been confined to the neck and axilla[19,153,211] or to the abdomen.[101] Nevertheless, invasion of the heart and mediastinal structures can be serious.[39,109,127]

Myositis and myocarditis. The presence of lymphorrhages in skeletal muscles of patients with myasthenia was first described by Weigert in 1901[183] and emphasized by Buzzard in 1905.[28] Since then these lesions have been found in the majority of autopsies of patients with myasthenia, but their significance has never been elucidated.

It is frequently said that lymphocytic accumulations are the sole abnormality and that there are no significant changes in the muscle fibers themselves.[1] Several authors, however, have reported myositic changes in myasthenia.[3,10,55,103,141,142] Similar lesions have been reported in patients diagnosed as having polymyositis or dermatomyositis, but who are said to have improved after the administration of prostigmine.[30,72,124,126] By some criteria, the latter cases suggest the diagnosis of myasthenia gravis.[138] There are also cases of otherwise typical myasthenia gravis associated with muscle wasting.[29,77,88,181] Three patients in the present series had clinically detectable atrophy of muscles of the shoulder girdle.

In the myocardium, isolated lymphorrhages have been observed several times[20,25,69,91,94,102,123,141,183] with or without slight alteration of muscle fibers. Necrotic and inflammatory lesions of the heart, similar to the cases reported here, have been recorded less frequently[4,10,55,103,135,141] and have sometimes been associated with polymyositis.

Although an infectious origin has been suggested[24,158] the significance of these inflammatory lesions remains obscure. Similar findings have been encountered in a variety of other conditions, especially hyperthyroidism,[41] rheumatoid arthritis, and collagen diseases.[31,35] One of the patients with myocarditis reported here was also pregnant, and similar lesions have been found in nonmyasthenic women dying during gestation.[60] Whatever the nature of these changes, the frequency with which they are encountered in myasthenia suggests that the relationship is more than coincidental and that any theory of pathogenesis must take them into account.

Convulsions. Although convulsive disorders in myasthenic patients have rarely been reported,[47,118,169] the incidence of 5 per cent among our fatal cases is representative of our experience in nonfatal cases.[75] The nature of this relation is uncertain but may be significant and will be treated in detail elsewhere.

SUDDEN DEATH

The character of death which has been designated as "sudden" was not instantaneous. Many patients, however,

who did not seem to be in danger at one moment did become cyanotic and mentally obtunded the next. In some patients the administration of prostigmine relieved these symptoms; in others temporary improvement followed respirator therapy; but in some death ensued within a few minutes. Sudden changes of this nature occurred in 24 patients, and ten of them had similar nonfatal attacks earlier. Although most of the patients who died suddenly had been admitted to the hospital because of myasthenic exacerbation, some early authors noted that similar deaths occurred when patients were in remission.[57,114]

The pathophysiology of these acute episodes is poorly understood, but they have been recognized as a feature of myasthenia gravis since the earliest descriptions.[46,57,79,114] In some instances, obstruction due to lingual weakness or pulmonary secretions may be important, and laryngeal obstruction is said to occur because of spasm of the glottis or vocal cord paralysis.[26,83,98,114,161] Since these phenomena are not always evident and since tracheotomized patients may die suddenly, obstruction is not always an integral part of the attack.

It has been suggested that exertion may cause sudden respiratory weakness[84] but the mechanism is obscure, although it has been stated that exercise of myasthenic muscle releases some curare-like factor.[66,159,160,171,178,187] Reflex bronchospasm may account for some cases in which dyspnea follows tracheal suction, bronchoscopy, or other manipulative procedures.

It is also possible that a cardiac mechanism may be responsible for sudden death,[95] but the suggestion that the heart may be involved in nonfatal myasthenia[5,18,50,133] has not been confirmed.[11,162] Electrocardiographic abnormalities in most of the reported cases can be explained by concomitant arteriosclerosis or hypertension,[7,143,184] and in the presence of respiratory muscle weakness, dyspnea and palpitation are not reliable indicators of cardiac disorder. The presence of myocarditis or myocardial lymphorrhages in some patients, however, suggests that myocardial lesions may sometimes be important. Even when structural lesions are lacking, vagal reflexes may induce cardiac arrest or ventricular fibrillation.[154,185] This may occur more readily in the presence of hypoxia and hypercapnia[38,54,156,157,192] and may be enhanced by eserine.[54] The cardiac effects of neostigmine[78] have been implicated as the cause of sudden death of nonmyasthenic persons who received the drug as a curare antagonist.[32,73,92]

The possibly important role of sedatives in these attacks is discussed below.

THERAPEUTIC CONSIDERATIONS

In recent years patients have died of myasthenia gravis despite an apparently rational therapy. This may be due to insufficient therapy, to overdosage of medication, to an inadequate understanding of the true clinical needs of individual patients, or possibly to complete failure of the therapeutic agents.

Neostigmine. Although other drugs have been used, neostigmine is still the drug of choice for the severely ill myasthenic. There is no evidence that any of the organic phosphates exert a more powerful effect on muscle strength than neostigmine; their delayed onset precludes use in emergencies and their long duration of action makes careful regulation difficult.[62,65] On the other hand, the brevity of action of Tensilon limits this drug therapeutically.[115] Most au-

thors do not favor the use of ACTH because increased weakness so often occurs [64,105,110] but some have reported benefit.[108] Although muscarinic symptoms may be less pronounced with pyridostigmine (Mestinon) than with neostigmine, experience with this new preparation is limited.[117,149,164] Preliminary observations suggest that it may be as good as, but probably not better than, neostigmine in the treatment of critically ill patients. Should it prove to be of value, the principles governing its use will probably be the same as for neostigmine.

It is our impression that several patients in the present series did not receive sufficient medication, but there are two problems in determining what constitutes sufficient medication.

The first of these is refractoriness to neostigmine. Viets[172] has stated that this is "merely an acknowledgment of inadequate dosage," but several of our patients received enough to suggest that further increments would have been of no value. One patient received 3.0 mg. per hour intravenously without significant effect, whereas a similar infusion one week earlier had produced dramatic improvement. Another patient received 95 mg. of neostigmine intramuscularly, 50 mg. intravenously, and 240 mg. orally within a period of 60 hours. During one hour she received 18.0 mg. intravenously with only slight and transient improvement. Failure to attain improvement, however, does not indicate that the drug is without effect, since withdrawal under these circumstances has resulted in worsening.

Refractoriness does not depend upon the amount of neostigmine administered nor the length of time it is given, and in this sense does not represent drug tolerance. There are some patients who have a clinical syndrome indistinguishable from myasthenia gravis but who never respond to neostigmine or related drugs.[137,138,179]

The second problem is toxicity. Muscarinic symptoms may be troublesome, due to increased gastrointestinal motility, sweating, bronchial secretion, and possibly bronchial spasm. More ominous is the possibility that overdosage may cause neuromuscular block, increasing weakness rather than correcting it. That this may occur has been demonstrated.[139] That it does occur in clinical situations is less certain; there have been reports of weakness apparently induced by organic phosphates.[63,189] Patients who are severely affected by the disease are the ones who receive large amounts of medication but are also most likely to have a crisis spontaneously. It is then difficult to determine whether the increased weakness is due to the disease or to the drug. The use of Tensilon in differentiating one form of weakness from the other[115] has not been uniformly successful. It is our impression that overdosage may become a serious consideration when the drug is administered parenterally, but probably not when the oral route is used. We would agree with Viets,[173] Harvey,[71] and Eaton[42] that in critical situations there is greater likelihood of administering too little rather than too much.

The following suggestions are offered as a guide to neostigmine therapy. If respiratory distress occurs and is corrected by parenteral neostigmine, the maintenance dose of oral medication should be increased, even if this is already large and even if the patient seems to be doing well between attacks. No definite statement can be made as

to the maximum permissible dose; some patients have taken as much as 2,500 mg. daily by mouth[164] or 576 mg. parenterally.[130]

When a patient who is receiving large amounts of neostigmine is placed in a respirator, the dose should be reduced. The toxic effects of the drug and the possibility that a partial effect might cause the patient to breathe out of phase with the machine led to the proposal[87] that neostigmine be completely withheld from respirator patients. Experience with several of our patients who have survived crises suggests that a period of abstinence may directly influence the return of sensitivity to the drug.[75] Theoretically, mechanical methods can provide adequate ventilation and, if proper precautions can be taken to prevent pulmonary complications, there is no obvious reason why a myasthenic patient in a respirator should not live indefinitely even without neostigmine. The success of this method in treating some patients[87,125] has demonstrated its practicality. Three patients in this series from whom the drug was withdrawn, however, had no complicating disease but died nevertheless. This indicates that there are aspects of therapy other than drug responsiveness which must be considered. There is not sufficient evidence to conclude that neostigmine should be completely withdrawn from every respirator patient, and it may be advantageous to continue the drug in amounts sufficient to insure cooperation, communication, coughing, and swallowing.

Atropine. We feel that the advantages of atropine medication considerably outweigh its theoretical dangers, although Schwab[147] has warned that in the presence of large amounts of atropine it may become impossible to distinguish weakness caused by the disease from that of drug toxicity. Unless muscarinic effects of anticholinesterase medications are blocked by atropine, one may not be able to administer sufficient medication to control dangerous weakness. Secondly, atropine is of value in blocking vagal reflexes affecting the heart and lungs.[59]

OMPA. Four patients in this series died while on OMPA therapy. This brings the total number of fatalities to 21 out of 62 patients treated with this substance.[61,80,116,131,146,189] This figure is weighted unfavorably as OMPA was tried by us and others on a number of patients who were seriously ill and did not respond sufficiently to routine medication. Our own cases showed little or no evidence of toxicity except for mild diarrhea, and it is our impression that the fatalities were not due to overdosage.

Sedatives. No direct causal effect can be implied because an extremely ill patient expired shortly after receiving a sedative. It is known, however, that restlessness, apprehension, and uncooperativeness, the symptoms for which sedation is frequently prescribed, may be manifestations of hypoxia and hypercapnia.[21,52,152] Eaton has pointed out that these symptoms sometimes respond to neostigmine.[42]

In the presence of hypoxemia and hypercapnia, the medullary respiratory center may be unusually sensitive to barbiturates[12] and less sensitive to its natural chemical stimulus, carbon dioxide, thus allowing hypercapnia to progress until its concentration is sufficient to be narcotic.[12,152] The dangerous effects of sedatives under these conditions have been demonstrated in dogs[12] and in humans suffering from asthma,[106,145,180] cor

pulmonale,[136] kyphoscoliosis,[81] pulmonary emphysema,[190] and poliomyelitis with respiratory failure.[21,52]

If the patient is already in the respirator, there may be less danger in administering sedatives to allay apprehension and to prevent the patient from breathing out of phase. If the symptoms for which sedation is required, however, are due to impaired gaseous exchange, it would be safer to be certain that the airway is patent and ventilation adequate.

Placebos. There may be considerable difficulty in evaluating emotional factors in patients seriously ill with myasthenia, but experience with two fatal cases described above illustrates not only the danger of administering placebos but also the fallacy of attempting to evaluate emotional elements in this way.

Maintenance of aeration. The cardinal principle of therapy in consideration of myasthenic crisis is the prevention of asphyxia. When the use of neostigmine fails, the mechanical respirator must be used, but the decision as to when this should be done may be difficult. Absolute criteria, like a critical value of the vital capacity,[121] which can be utilized in progressive neuromuscular disorders like poliomyelitis and polyneuritis, are less valuable in myasthenia. Frequently, respiratory embarrassment in myasthenia may be reversed by adequate amounts of neostigmine. On the other hand, one should not await the appearance of cyanosis, apnea, or coma before starting therapy. When in doubt, the respirator should be used. Provision should always be made for unexpected respiratory failure or obstruction in the treatment of any patient who has suffered a recent exacerbation; intratracheal tube, laryngoscope, tracheotomy set, suction apparatus, and respirator should always be on hand.

Most patients, if not all, who have dysphagia, dysarthria, or vocal weakness and are to be placed in a respirator should have a tracheotomy. If changes occur too rapidly to permit this electively, endotracheal intubation and positive pressure respiration may afford time to place the patient into the respirator.

For patients in the respirator, constant attention to pulmonary status is mandatory. Plum[121] has described in detail the importance of frequent turning, postural drainage, antibiotic therapy, careful suctioning, and bronchoscopy. Direct measurement of tidal air and periodic estimations of arterial oxygen, carbon dioxide, and pH may provide guides to optimal stroke pressures. Exsufflation with negative pressure[8] has been of value in clearing obstruction in the small bronchioles beyond reach of the bronchoscope.

The object of respirator therapy in myasthenia is to tide the patient through the period of crisis, in the hope that strength and response to neostigmine will return. However ominous the situation may appear, it should be recalled that some patients have survived many months of respirator therapy and enjoyed significant remissions thereafter.[80]

SUMMARY

1. In a series of 180 patients with myasthenia gravis observed since 1930, there has been a known mortality rate of at least 30 per cent. The average duration of symptoms among 39 fatal cases was 2.8 years. This group may represent a more malignant form of the disease than is usually encountered.

2. Thirteen patients died suddenly and unexpectedly; several patients had acute episodes of dyspnea which were

relieved by neostigmine prior to the final attack. It is suggested that these attacks should be recognized as premonitory; the maintenance dose of neostigmine should be increased and all precautions taken.

3. Sixteen patients were in a mechanical respirator at the time of death. All but two of them suffered considerable anoxic insult prior to the institution of respirator therapy, and among those examined at autopsy pulmonary pathology was universal.

4. Several patients showed little or no response to large amounts of neostigmine in the terminal phases and the question of neostigmine refractoriness is discussed.

5. The use of barbiturates, opiates, and placebos in patients with ventilatory insufficiency who are not in a respirator may be dangerous.

6. Possibly fatal complicating diseases were present in ten patients, but muscle weakness played a prominent role in the circumstances preceding death. Two deaths were associated with pregnancy and two with thyrotoxicosis; the variable influences of these conditions on the course of myasthenia are discussed.

7. Respiratory infections preceded the terminal crisis in ten patients; there was no overt precipitating illness in 17 others.

8. Thymomas occurred in nine of 26 patients examined at autopsy, hyperplasia was present in six, no thymic tissue was found in eight, and three were normal.

9. Lymphorrhages occurred in the muscles of 15 patients. Nodular myositis was present in three, extensive myocarditis in two, and focal myocarditis in one. The significance of these lesions for theories of the pathogenesis of myasthenia gravis is discussed.

10. Pulmonary pathology was present in all but four autopsied patients.

11. The following elements of treatment are stressed:

a) Recognition of premonitory attacks of respiratory distress.

b) Provision of adequate medication.

c) More cautious use of sedatives.

d) Early institution of mechanical respiration with attention to adequate gas exchange.

e) Control of electrolyte balance.

f) Control of infection.

The authors are indebted to Dr. Arthur Purdy Stout who reviewed the histologic sections of thymus, to Dr. Abner Wolf who reviewed some of the muscle specimens, and to Dr. J. P. Flynn who allowed us to use material in the necropsy files of the Presbyterian Hospital.

The list of references documenting this paper is omitted here because of limitations of space, but will be included in the authors' reprints.

Interseizure Disturbances in Focal Epilepsy

Frank Morrell, M.D.

THE ACTIVITY of an epileptogenic focus has been likened to the glowing of an ember in the fireplace.[1] At intervals the ember is fanned into flame which, spreading, produces first its aura and then perhaps, recruiting the sensitive tissues about it, its characteristic seizure. This parable has its electrographic correlation in the demonstration in the electroencephalogram of a constant discharging focus of abnormal activity, sharply localized during the interseizure periods, perhaps remaining so for days, weeks, or months, but then suddenly spreading in a characteristic pattern as the seizure begins.

What is the effect of this continually discharging lesion on normal brain physiology? What does it do in the intervals between the sudden excessive paroxysmal discharge which results in the convulsive seizure?

It is a well known observation that patients with seizures due to demonstrable organic brain damage often show interseizure abnormalities in the form of behavior disturbances or mental deterioration. In some, of course, one can find abnormalities of motor or sensory function demonstrable on neurologic examination. But even in the absence of this, it is possible to demonstrate impairment on psychologic testing[2] and on clinical examination with regard to general alertness and performance at school and play.

Many explanations have been advanced to account for these interseizure disturbances. The effect of medication, frequent larval seizures, metabolic changes due to long-continued convulsions, vascular alterations and secondary atrophy, gross loss of cerebral tissue, and important psychologic factors all undoubtedly play a role. However, as a result of experiences with the surgical therapy of focal epilepsy and cerebral palsy, another and perhaps more important factor has been defined. It has been noted that surgical ablation of epileptogenic foci results not only in improvement with regard to seizure control, but is often followed by marked improvement in intellectual functioning and in general behavior. This occurs despite the fact that, in the removal of such foci, a considerable amount of surrounding normal tissue must be sacrificed, re-

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sulting in a loss of far more cortical substance than is involved in the lesion itself. Penfield[3] has postulated that the diseased cortex exerts a "nociferous" influence upon the function of the brain as a whole, the influence extending far beyond the anatomic confines of the actual lesion and far beyond its effect as an epileptogenic agency.

Most attempts to measure alterations in human brain function in interseizure intervals have utilized complex psychologic tests which measure brain performance as a whole or such unlocalized variables as memory.[4] However, the electrical discharge which designates the diseased cortex may be sharply localized to functionally specialized areas. Its effect may be confined to the function represented in the region primarily involved by the epileptiform activity. Our problem, therefore, was to find a means of measuring disturbance in function of specific cortical regions or systems in the hope of explaining the day-to-day impairment of function induced by so-called "nociferous" cortex.

METHODOLOGY

Certainly one of the primary functions of higher nervous activity is the establishment of temporary connections or links between functionally specific cortical regions. For example, learning a musical score requires the establishment of definite relationships between visual and auditory receiving and integrating areas. Playing the score requires connection to the motor strip. The semiautomatic act of walking requires constant interplay between sensory (proprioceptive) and motor zones.

In the present study we have examined two such forms of temporary connection or linkage involving specific sensory modalities and have determined the effect on these connections of a discharging lesion implicating the primary receiving area for one modality.

1. *Conditioned alpha rhythm*

The 8 to 13 c/sec. alpha rhythm in man normally "blocks" to a visual stimulus and does not normally respond to a sound of sufficiently low intensity or to a light touch. However, by constantly pairing a touch or tone stimulus with the visual one, the alpha can be conditioned to respond to touch or tone alone. Such conditioning requires the establishment of new, "learned," temporary connections between auditory or tactile receiving areas and the visual receiving-integrating system. In anatomic terms, this probably links the temporal or parietal regions with the occipital lobes. Finally, successful conditioning is a measure of the functional integrity of the respective receiving and associative stations and of the capacity of these linked areas of cortex to mutually participate in new, learned physiologic behavior.

Previous studies have shown that the conditioned alpha reaction in an adult can normally be established to either touch or sound in from two to 20 paired trials. The detailed technic of conditioning has been described previously.[6,7] Essentially, it consists in using a bright white light placed one foot in front of the subject's eyes and covered with a diffusing screen for the unconditioned stimulus and a light touch to the left arm or a low intensity tone (1024 c/sec.) as the conditioned stimulus. The latter is delivered to a loud speaker situated above and behind the subject so that the sound impinges on both ears approximately simultaneously. The precise intensity is determined by the level at

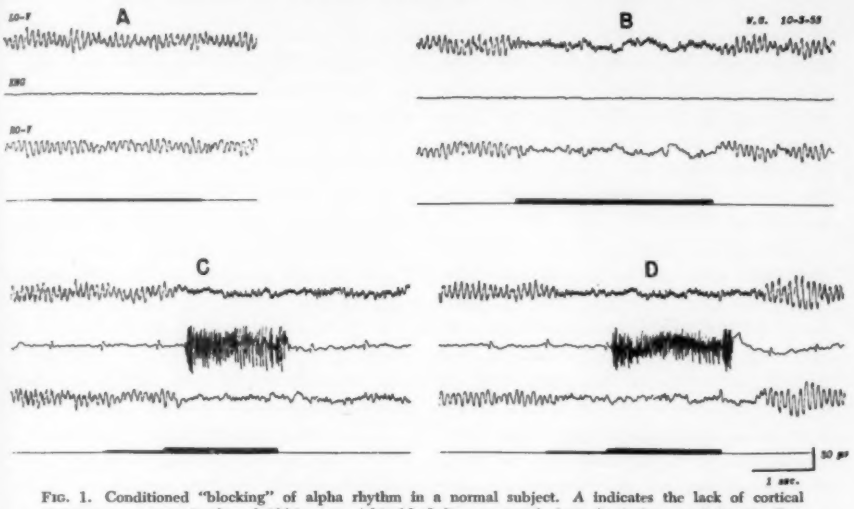

FIG. 1. Conditioned "blocking" of alpha rhythm in a normal subject. *A* indicates the lack of cortical response to a tone stimulus of 1024 c/sec. (thin black line on signal channel), before conditioning. *B* is the response to bright light (thick black line on signal channel) before conditioning. *C* is the first paired trial showing no response to the tone but prompt "blocking" when the light appears. *D* is the ninth trial and demonstrates the fully developed conditioned alpha blocking. The alpha desynchronization occurs in response to the tone, considerably before the light stimulus is presented. An electromyogram, recorded via surface electrodes from the right forearm, was used to measure visuomotor reaction time. There is an electrocardiographic artifact in that channel.

which there is no evident cortical response to the tone alone. It will vary somewhat from subject to subject.

The tone or touch is presented alone for one second. It is then overlapped by the light which continues for two seconds, making a total stimulation time of three seconds. Both stimuli go off together. A conditioned response is considered established when alpha "blocking" occurs to four successive presentations of the conditioning stimulus.

Figure 1 demonstrates the typical simple conditioned alpha response. *A* shows a low intensity tone stimulus (1024 c/sec.) presented before conditioning. There is no evident "blocking" of the alpha rhythm. *B* indicates the unconditioned blocking response to bright white light directed into the retina. *C* is the first paired trial showing no response to the tone but prompt "blocking" when the light appears. *D* is the ninth trial where the "blocking" reaction now appears in response to the tone and before the light is presented.

2a. *Simple motor reaction time*

In the experiment shown in figure 1 the subject is asked to clench his fist as quickly as possible after the light is perceived. The muscular response is recorded from surface electrodes placed upon the right forearm. In this way a measurement of visuomotor reaction time is obtained with each reinforcement of the conditioned response. Reaction time to auditory and tactile stimuli was measured separately from the conditioning situation.

The measurement of motor reaction time to visual, auditory, and tactile stimuli provides a test of both the existence

of links from the primary receiving areas to the motor strip and, more important, of the conduction time involved in making the connection. The latter has been shown to be quite sensitive to alterations in cerebral function.[5]

2b. *Visuomotor reaction time after experimental extinction*

The motor reaction time to light was measured after extinction of C - R by nonreinforcement. This provides a cross-check on the establishment of true conditioning, because in previous studies[6] it had been shown that extinction of C - R induces a central inhibition, which is reflected in a prolonged visuomotor reaction time. If conditioning had been established and then extinguished, the necessary inhibitory process should be reflected in a prolonged reaction time. If none or poorly established conditioning was present, then extinction should cause no (or lesser) prolongation of visuomotor reaction time.

Figure 2 demonstrates the connections presumed to be involved. The heavy arrows indicate the linkage involved in reaction time, while the interrupted arrows denote the conditioned connection. Of course, the arrows indicate only origin and terminus of the linkage and not the path of the impulses.

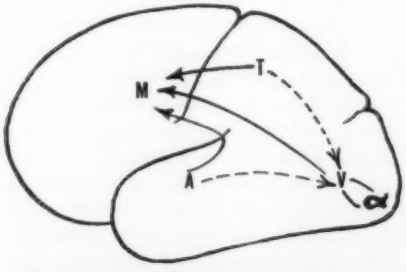

FIG. 2. Schematic representation of the connections involved in the present study. The solid lines represent the linkages established in the motor reaction times. Interrupted arrows denote the conditioned connections. Both visual cortex and "alpha region" are indicated in the diagram, since the visual receiving area is not necessarily coextensive with the cerebral tissue responsible for generation of the alpha rhythm.

MATERIAL

A total of nine patients with temporal lobe lesions have so far been studied and form the basis of this report. The patients were selected on the following clinical and electrographic criteria.

1. The presence of a spike or sharp wave focus, localized to the temporal lobe on either side, and visible on the unactivated electroencephalogram.

2. Present and past history of seizures, either typical psychomotor in type or beginning with definite gustatory, olfactory, or auditory aura. A psychomotor seizure was defined as one beginning with searching movement of eyes and head, followed by automatic behavior, usually sucking or masticatory, sometimes speech arrest, and with postictal amnesia.

All nine patients were between 18 and 55 years of age; six were male and three female. In all patients hearing was audiometrically tested and found to be intact; vision was correctible to 20-20 with glasses. Two patients were left-handed from birth; the remainder were right-handed; none had had an induced change in handedness. Four patients had electrographic lesions in the left anterior temporal region, two in the left posterior or midtemporal area, and three in the right anterior temporal region. Craniotomy was carried out in four cases. Two had definite cicatrix with localized atrophy; one had a sphenoid ridge meningioma. In one case no abnormal tissue was found, but seizures ceased after the removal of the electrical focus. All of these cases were examined

TABLE 1
COMPARISON OF TRIALS TO CONDITION AND REACTION TIME IN SECONDS

Case	*Location*	*Trials to Cond.*		*Motor Reaction Time in Seconds*		*Motor Reaction Time to Light Following Extinction of C - R to*	
		Tone	*Touch*	*Tone*	*Touch*	*Tone*	*Touch*
E. C.	LAT	107	12	.15	.2	.2	.9
G. F.	LAT	16	11	.2	.22	1.0	1.2
M. L.	LAT	200 pr. not cond.	16	.3	.28	.3	.6
R. H.	LAT	33	8	.2	.2	.9	.9
L. L.	LPT	200 pr. not cond.	22	.35	.3	.35	.65
H. R.	LPT	200 pr. not cond.	17	.2	.2	.3	.55
B. C.	RAT	200 pr. not cond.	4	.14	.2	.2	.8
H. B.	RAT	76	7	.19	.15	.45	.9
J. S.	RAT	52	4	.19	.15	.5	1.2

prior to surgery. None have died. Finally, all cases were on anticonvulsant medication with great variation in degree of control.

RESULTS

Table 1 demonstrates the following findings:

1. Definitely impaired alpha conditioning to the tone stimulus, as opposed to a normal response when touch is the conditioned stimulus. Though there is wide variation in the number of trials required to establish conditioning in both groups, there is an overlap in only one patient.

2. There is no difference in the motor reaction time to touch and to tone stimuli.

3. Measurement of motor reaction time to light after experimental extinction shows the delay to be much more pronounced after extinction of a C - R to touch; that is, the better established the C - R, the greater the inhibitory process required to obliterate it. The delay is much less following extinction of C - R to tone. It is noteworthy that where the visuomotor reaction time after extinction of tone C - R is prolonged, there was also other evidence of good conditioning, for example, normal number of trials in one (G. F.) and only slightly more than normal in the other (R. H.).

DISCUSSION

The data indicate that the focal epileptogenic lesion selectively impairs the kind of temporary connection involved in the conditioned reflex and does not impair the temporary connection involved in motor reaction time. The impairment is further selective in that it does not involve all C - R's but only that which requires the cortical region physiologically damaged by the discharging focus. It will be noted that impairment in formation of C - R's to sound is not an all-or-none phenomenon, but shows wide variation in degree. In one patient with a left anterior temporal

focus, it was possible to establish conditioning to tone within a normal trial period (G. F.); one patient with a left posterior temporal focus showed some impairment in conditioning to touch as well (L. L.). Note that in this latter case it was completely impossible to condition the alpha to sound, and that reaction times, though equal to the two stimuli, were consistently at a somewhat higher than normal level, suggesting perhaps a more generalized disturbance involving parietal lobe as well. Since we have no way of knowing from an electroencephalographic focus how much of the auditory cortex is involved, it is likely that the degree of impairment in formation of C - R's is an objective measurement of the degree of physiologic impairment of the auditory cortex, or at least of that portion of auditory cortex representing the specific tone stimulus used. It is also possible that the degree of impairment may reflect the time necessary to find other available pathways to achieve the necessary linkage. In more massive damage even alternative pathways are perhaps closed.

One further observation from these data is that the greatest impairment was seen in the patients with posterior temporal lesions in the dominant hemisphere. Trials necessary for conditioning to the touch stimulus were also greater in number than usual and, as judged by the figures in the last column of table 1, the reflex established to the touch stimulus was less stable than in the other cases. In line with this, it has been shown by Papez,[8] Walker,[9] and Jasper, Marsan, and Stoll[10] on both anatomic and physiologic grounds that the posterior temporoparietal cortex, situated between the three great sensory receiving stations, functions as an integrating center for all primary sensation. Large to-and-fro fiber tracts relate this cortex to lateral and posterior nuclei of the thalamus and to reticular networks in diencephalon and brainstem. It is not surprising that a physiologic lesion of this area results in a somewhat more generalized disturbance of integrative activity. Unfortunately, we have no cases for comparison with homologous lesions restricted to the nondominant hemisphere.

Finally, some information as to the pathways involved may be inferred from the fact that leads taken independently from the two occipital lobes show no differences in the alpha response, though in each case the electrical disturbance was unilateral. Some part of the pathway, therefore, must include central distributive systems and cannot be simple transcortical spread along the hemisphere.

The lack of any delay in cortical conduction time as demonstrated by the normal motor reaction time suggests that the mechanism for this kind of temporary connection is distinct from that implicated in the C - R. It may also be true that separate anatomic areas are involved, but it seems likely that at least one part of the pathway is held in common – that of the primary auditory receiving area. Also, since the motor response is a voluntary one, it is not likely that the entire pathway remains in subcortical circuits.

The retained capacity to form C - R's from the electrographically intact parietal cortex indicates a striking selectivity of the pathologic process. It would be of interest to determine whether this could be carried to tones of varying pitch or intensity, perhaps thus differ-

entiating separable lesions, even within the auditory cortex itself.

It is interesting that the defect in cortical physiology shown here is one of primary importance in determining the ability of the organism to adjust to a changing environment. It is not at all surprising that such an impairment in cortical function might result in far-reaching changes in mental efficiency and in behavior. These are precisely the changes so often seen in epileptic patients. Poor judgment, inability to learn from experience, decreased attention span, all might be explained by these data. Furthermore, with relatively small isolated foci one might expect fairly good compensation for such a defect. This, too, is consistent with what we know of the epileptic patient.

Undoubtedly, the mechanism postulated here is not the only cause of the mental deterioration and behavioral disorders seen in symptomatic epilepsy. Certainly, all of the other factors mentioned previously play an important role. It would seem, however, that the capacity to form significant temporary connections must have a high survival value for the organism. The impairment of this capacity in focal epilepsy may very well account for much of the interseizure symptomatology and may to some extent explain the phenomenon of "nociferous cortex."

SUMMARY AND CONCLUSIONS

It has often been pointed out that patients with seizures due to focal cortical lesions frequently show interseizure abnormalities in the form of behavior disturbances or mental deterioration. The diseased or "nociferous" cortex apparently exerts a constant deleterious effect on brain physiology. It was felt that this might be reflected in demonstrable functional impairment specific for the area of cortex involved by the lesion.

In patients with sharply localized temporal lobe spike foci and with clinical seizures, either psychomotor in type or with an aura suggesting temporal lobe origin, investigations of cortical function involving the auditory system were undertaken. Two kinds of measurement were made: 1) the capacity to form a conditioned alpha response to a tone was compared with that to a tactile stimulus, and 2) the motor reaction time to tone was compared with that to touch.

Our results indicated that there was a marked impairment in the ability to form a conditioned alpha response to a sound stimulus in patients with temporal lobe lesions. However, the motor reaction time in these patients was unimpaired to both the tone and tactile stimulus.

Thus the focal epileptogenic lesion selectively impairs the kind of temporary connection involved in establishing a conditioned reflex, but does not impair the kind of temporary cortical connection involved in the voluntary motor reaction to a stimulus. It is felt that impairment in the capacity of damaged cortex to participate in the formation of conditioned reflexes may explain much of the interseizure symptomatology of patients with focal epilepsy.

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■ The symptoms of injuries or alterations of the spinal cord consist in various degrees and forms of paralysis of voluntary movement; in a diminution or loss of the various kinds of sensibility, as regards contact, temperature, tickling, muscular sense, pain; in involuntary movements – spasmodic, choreic, epileptiform, etc.; in a morbid increase of the various kinds of sensibility; in a perversion of sensations; in errors as to the place of starting of a sensitive impression; in the referring of sensitive impressions to the extremities of the conductors of these impressions; in the absence, diminution, or increase of the reflex faculty, etc.

Paralysis of voluntary movement may occur in consequence of alterations existing almost anywhere in the spinal cord. This may seem to be very strange, particularly when we remember that a transversal section of the posterior columns of the spinal cord, in animals, is without influence upon voluntary movements. What are the deductions to be drawn from pathological cases observed in man as regards the share of the posterior columns of the spinal marrow in voluntary movements? Three questions must be examined in this respect: First, are there nerve-fibres going to muscles, and employed in voluntary movements, passing along the posterior columns, from the encephalon down to the spinal nerves? Are there volitional-motor nerve-fibres passing, for a short distance, through the posterior columns? Are there some peculiar causes of diminution of voluntary movements in cases of alterations of the posterior columns?

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Analysis of Autonomic Hypothalamic Functions in the Intact Organism*

E. Gellhorn, M.D., Ph.D.

THE FUNCTIONAL PSYCHOSES have been the object of neurophysiologic research during the past 25 years. The aim of these studies was mainly twofold: 1) to determine, particularly under conditions of stress, the physiologic deviations of psychotics, especially schizophrenics, from standards obtained through tests on normal individuals, and 2) to analyze the mechanism involved in the so-called shock therapies of mental diseases.[1,2,3]

The work of numerous authors, particularly that of Hoskins and colaborators,[4] suggested that schizophrenics show a deficient reactivity of sympathetic centers. This was shown by the lessened reactivity of the sympathetic system to cold and heat stress, in postural cardiovascular adjustment reactions, and insulin hypoglycemia. The "sluggish sympathetic reactivity" is further illustrated by the failure of these patients to show a rise in blood sugar or a lymphopenia in emotional excitement, although these changes occur just as in nonpsychotic individuals if lower sympathetic centers are stimulated.[2,5] The observations suggest strongly that in these conditions the hypothalamus and not the medulla oblongata are involved.

These are just a few examples of research which point to an inadequate responsiveness of the sympathetic system, at the hypothalamic level, in functional psychoses. The deficient sympathetic reactivity leads to a disturbance of the autonomic balance, which was indicated in our earlier studies[6] by a relative dominance of the vago-insulin system.

The second neurophysiologic approach to the problem of functional psychoses was made through an analysis of the physiologic mechanism involved in several apparently dissimilar procedures such as insulin hypoglycemia, electroshock, and Metrazol-induced convulsions. It was found that these procedures had one important feature in common, the excitation of the centers of the sympatheticoadrenal system.[1] This excitation resulting from repeated application of shock therapy persists for a considerable period of time.[7] It was suggested[1,2,3] that improvement in func-

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*Dedicated to Sir Francis Walshe in honor of his seventieth birthday.

tional psychoses following shock therapy was linked with the increased sympathetic reactivity of the hypothalamus and the consequent alteration of the hypothalamic-cortical discharge which mirrors the sympathetic downward discharge.[5]

Since it was shown experimentally that hypothalamic-cortical discharges modify the responsiveness of the cortex as a whole, alter sensations and perceptions initiated by specific sensory impulses,[8,9,10] change the reactivity of the motor cortex to electrical stimulation,[11] and evoke profound changes in conditioned reactions,[12] it may be expected that behavioral changes result from changes of the autonomic hypothalamic reactivity and balance.

Even if it were granted that the action produced in the brain in shock therapy is essentially that of stimulating sympathetic centers, the theory presented here has still two great defects: 1) a broader foundation is needed to show that the discussed changes of central sympathetic reactivity play an important role in the disease process, and 2) patients with functional psychoses were treated in this and earlier discussions as a rather uniform group in which a significant number showed signs of a deficient sympathetic reactivity, but the clinical material is certainly more complex.

Granting that the existence of a deficient central sympathetic reactivity appears to be well established, the proof that this factor plays a significant role in the disease process was, until recently, rather inadequate at least numerically. However, important contributions were made by Jahn,[13] Solomon and co-workers,[14] and Hill[15] who indicated that increased sympathetic reactions accompanied clinical improvement. Then Funkenstein, Greenblatt, and Solomon[16] published the results with their Mecholyl test. They found in a large number of patients that improvement of the clinical condition of the patient is associated with an alteration of the blood pressure reactions that are induced by Mecholyl. They also found that such improvement was not related to the clinical diagnosis but to the type of the blood pressure reaction induced by Mecholyl. This, in the author's opinion, suggests the basic importance of the autonomic disturbances in the disease process and makes it imperative to attempt, through a neurophysiologic analysis, to understand the significance of the Mecholyl test.

The chief clinical finding with the Mecholyl test may be described as follows. Whereas on injection of 10 mg. Mecholyl intramuscularly 80 per cent of normal individuals show a moderate fall of the blood pressure and a return to the control level in about eight or ten minutes, such a reaction is seen only in 20 per cent of the psychotic group. The remaining 80 per cent show either a lesser hypotension followed by a distinct overshooting of the blood pressure, or a greater and prolonged hypotension so that even after 20 minutes the original level of the blood pressure has not been restored. These results have been confirmed on about 190 patients. They indicate that, in a high percentage of neuropsychiatric cases, autonomic disturbances exist which are measurable by a simple vascular test. Our experiments showed, in addition, the reliability of the test. The type of blood pressure curve resulting from the injection of Mecholyl could easily be reproduced in the same patient if the test was repeated in an interval of eight to ten days.

It is the task of this paper to describe the experimental work in which the correlation existing between a central autonomic disturbance and the alteration of the Mecholyl and other autonomic tests was established. On the basis of this study it was endeavored to develop methods by which central autonomic disturbances can be recognized in the intact organism.

THE MECHOLYL REACTION AND THE SYMPATHETIC SYSTEM

It is well established that when the pressure in the sino-aortic area is lowered through mechanical or chemical means, increased sympathetic discharges ensue which have the tendency to counteract the experimentally induced hypotension. If in different organisms the same amount of a hypotensive drug elicits as widely different actions on the blood pressure as were described by Funkenstein and co-workers[15] and confirmed by ourselves, the most probable cause of the differences seems to lie in the reactivity of the centers of the autonomic nervous system which respond to a fall of the blood pressure. Heretofore these centers were thought to be located in the medulla oblongata. It seems, however, to be very unlikely that the autonomic dysfunctions of psychotic patients would reside in the medulla oblongata. On the contrary, clinical and experimental experiences suggest an involvement of the hypothalamus which is closely linked with emotion and behavior and controls practically all known autonomic reactions.

It was therefore assumed that the three types of responses to Mecholyl – 1) slight hypotension followed by overshooting, 2) moderate hypotension with return to control level within ten minutes, and 3) marked hypotension with greatly delayed return of the blood pressure* – would be due to different degrees of responsiveness of the sympathetic system at the hypothalamic level. This system is called into action when a fall of the blood pressure is induced peripherally, as in the Mecholyl test. This assumption was validated by the following experiments performed in lightly anesthetized cats.[17–19]

1. Mecholyl, acetylcholine, and histamine were injected intravenously before and after the excitability of the posterior (sympathetic) hypothalamus had been altered by the injection of minute quantities of drugs into this structure. The excitability of the sympathetic division of the hypothalamus was determined by stimulation with square wave currents and its action on the blood pressure, pulse rate, and contraction of the nictitating membrane. If, through intrahypothalamic injection of Pentothal, the sympathetic hypothalamic excitability was diminished, the hypotensive action of Mecholyl and other hypotensive drugs was aggravated and prolonged, comparable to a shift from type 2 to type 3. That a diminished sympathetic hypothalamic response was involved was indicated by the fact that the delayed return of the blood pressure to the control level was accompanied by a lesser contraction of the nictitating membrane than was seen in the control test performed before the intrahypothalamic injection of the drug.

2. If, on the contrary, drugs such as Metrazol were injected intrahypothalamically, leading to an increased excitability of the posterior hypothalamus, the hypotensive action of Mecholyl was less-

*These responses are referred to later as blood pressure curves or types 1, 2, and 3, respectively.

ened and was often followed by a hypertensive phase, that is, a shift occurred from type 3 to type 2 or even to type 1. At the same time the changes in the pulse rate and the nictitating membrane which accompany the action of the hypotensive drugs indicated a greater sympathetic responsiveness.

3. Physiologic variations in the state of excitability of the posterior hypothalamus were likewise reflected in the responsiveness of the blood pressure to hypotensive drugs. If the posterior hypothalamus was stimulated with a subthreshold electrical stimulus, the action of Mecholyl was altered, as in the above described experiments, with injection of Metrazol into the posterior hypothalamus. Similar changes were observed to occur during a "spontaneous" arousal reaction seen occasionally during a state of "light" anesthesia.

4. The observations described in 1–3 were reversible. They show in a variety of conditions that the sympathetic excitability of the hypothalamus determines the hypotensive action of Mecholyl and other hypotensive drugs and, particularly, the speed of return of blood pressure to the control level. It should be added that the sites of the intrahypothalamic injection experiments were determined histologically. They were located immediately anterior to the mammillary bodies in most instances; a few sites were in the infundibulum and some in the mammillary bodies.

5. In a final series of experiments lesions were produced through high frequency currents in the posterior hypothalamus and the effect of these lesions was studied on the action of hypotensive drugs.[18] In 17 cats lesions were placed successfully in the posterior hypothalamus, and in all but two experiments* return of the blood pressure from the hypotensive action was distinctly delayed and acceleration of the pulse rate and contraction of the nictitating membrane were diminished. On the other hand, lesions placed in the thalamus failed to alter the drug-induced hypotensive action. If lesions extended from the posterior hypothalamus into the midbrain, the effect was the same as in those lesions which were confined to the posterior hypothalamus. It is interesting that in a few instances even unilateral lesions in the posterior hypothalamus distinctly delayed return of the blood pressure from the acetylcholine- or histamine-induced hypotension.

It may be concluded from these investigations that, other conditions being equal, the hypotensive actions of Mecholyl and similar drugs is determined by the excitability of the sympathetic division of the hypothalamus. The experiments suggest strongly that interindividual variations in the effectiveness of a given dose of Mecholyl and also variations in the effectiveness of this drug in the same individual, for instance before and after a certain treatment, are to be accounted for by differences in the central sympathetic excitability at the hypothalamic level.

THE NORADRENALIN TEST AND THE PARASYMPATHETIC SYSTEM

It is obvious that an extension of this work to include determination of responsiveness of the parasympathetic division of the hypothalamus would be of considerable theoretical and clinical value. Since a fall of the blood pressure has been shown to elicit a sympathetic discharge (via the baroreceptors),

*These two showed no significant changes.

which depends on the excitability of the hypothalamus, and since the baroreceptor reflexes involve (reciprocally) both branches of the autonomic nervous system, it appeared reasonable to investigate the dependence of the parasympathetic reflexes elicited by a rise of the blood pressure (and consequently of the sino-aortic pressure) on the excitability of the parasympathetic (anterior) division of the hypothalamus. Experiments were performed in which noradrenalin was injected intravenously and the degree of the pulse slowing for a given rise of the blood pressure was determined before and after the excitability of the anterior hypothalamus had been altered experimentally. Two groups of experiments were performed.

In the first group Pentothal was injected into the anterior hypothalamus,[17] whereas in the second group high frequency lesions were placed into this structure. The sites of the injections were just above the optic chiasma; the lesions were found in the area between the optic chiasma and the anterior commissure.[19]

Following injection of Pentothal the slowing of the heart rate which accompanied the noradrenalin-induced rise of the blood pressure was greatly reduced. This occurred even in those experiments in which the pressor effect of noradrenalin was greater than in the pre-injection control test. In several experiments it could be shown that even larger concentrations of noradrenalin could not reduce the heart rate to the degree seen in the noradrenalin test under control conditions. But 20 to 30 minutes after the intrahypothalamic injection, the Pentothal effect disappeared and the original pulse-slowing response was restored.

The results produced by lesions in the anterior hypothalamus were similar. The noradrenalin-induced pulse-slowing reflex was distinctly reduced after bilateral and occasionally after unilateral anterior hypothalamic lesions. However, these effects were not reversible under the conditions of an acute experiment.

DETERMINATION AND CHARACTERISTICS OF THE AUTONOMIC HYPOTHALAMIC BALANCE IN THE INTACT ORGANISM

Autonomic reflexes, for instance those elicited via the sino-aortic baroreceptors, show reciprocal behavior.[2] Thus the noradrenalin-induced pressor effect causes a slowing of the heart rate through increased vagal and decreased sympathetic discharges. These data raise questions concerning the mutual influence of the parasympathetic and sympathetic divisions in the autonomic centers in general and in the hypothalamus in particular, especially whether the sympathetic division of the hypothalamus holds the parasympathetic division in abeyance and vice versa. This problem can be investigated by determining anterior and posterior hypothalamic excitability with the noradrenalin and Mecholyl tests, respectively, before and after a hypothalamic imbalance has been created by a lesion in either the anterior or the posterior hypothalamus.[19]

Experiments showed that after a posterior hypothalamic lesion there was not only intensification of the hypotensive action of Mecholyl and histamine associated with a lessened sympathetic reflex reactivity, but a stronger pulse-slowing reflex in response to noradrenalin than under control conditions. These results suggest that anterior hypothalamic functions are released when, as the consequence of a posterior lesion, the activity of the posterior hypothalamus is lessened.

The following experiment shows that this interpretation is correct. The increase in the pulse-slowing reflex, which occurred after a posterior hypothalamic lesion, was eliminated when Pentothal was injected into the anterior hypothalamus. However, 20 to 30 minutes later after the action of the drug had worn off, the noradrenalin-induced pulse-slowing reflex was again greatly magnified.

Similar experiments were performed on the effect of anterior hypothalamic lesions on the function of the posterior hypothalamus as measured by the hypotensive drug test. The blood pressure curve, acceleration of the pulse rate, and height of the contraction of the nictitating membrane indicated a greater sympathetic responsiveness to acetylcholine and histamine and thereby gave evidence that the sympathetic responsiveness was greatly increased after an anterior lesion. This likewise suggests that the anterior hypothalamus holds the sympathetic functions of the posterior hypothalamus in check. Consequently, with diminution of the parasympathetic anterior hypothalamus activity following a lesion in this structure, the posterior hypothalamus is released.

This release can be demonstrated also by testing posterior hypothalamic functions through direct electrical stimulation. It is then seen that sympathetic responsiveness, as indicated by rise of the blood pressure, the contraction of the nictitating membrane, and the acceleration of the heart rate is greater after an anterior lesion than under control conditions.

The experiments show that anterior hypothalamic lesions cause a release of posterior sympathetic functions as demonstrated by the augmented response of the posterior hypothalamus to reflex and direct stimulation. Conversely, posterior hypothalamic lesions lead to a release of anterior parasympathetic functions indicated by reflex stimulation. It is inferred from these experiments that physiologically parasympathetic and sympathetic functions behave reciprocally at the hypothalamic level.

CLINICAL IMPLICATIONS

The experiments described in the preceding sections have shown that the blood pressure effect of Mecholyl depends on the excitability of the sympathetic hypothalamus. A change from the blood pressure curve 3 to 2 and then to 1 indicates, therefore, an increased sympathetic responsiveness, whereas a change in the reverse direction appears to be due to a progressive diminution of the sympathetic responsiveness of the hypothalamus.

The finding of Funkenstein, Greenblatt, and Solomon[16] that in the majority of cases electroshock causes in type 3 clinical improvement, which is associated with a shift in the Mecholyl test to type 2, is of great interest from the point of view of our investigations. It means that electroshock treatment leads to an increased responsiveness of the sympathetic division of the hypothalamus. This conclusion is in agreement with the work of Gellhorn and Safford[7] that repeated electroshocks increase central sympathetic reactivity and that this effect persists for prolonged periods of time in the experimental animal. Since type 2 represents the type of response found in the majority of normal individuals, it may be said that the change from a deficient to a normal sympathetic hypothalamic reactivity is associated with clinical improvement in certain

neuropsychiatric cases.

In the light of this interpretation it is not surprising that the administration of electroshock treatment in patients of types 1 and 2 was unsuccessful. It would either produce an autonomic imbalance in patients whose Mecholyl test was normal (type 2) or further augment the imbalance in patients belonging to type 1. Obviously, electroshock treatment of patients with a normal or hyper-reactivity of the sympathetic hypothalamus is physiologically unwarranted.

It follows from this discussion that, in disturbances of the sympathetic division of the hypothalamus, procedures should be applied which tend to restore normal sympathetic reactivity (indicated by the reaction type 2 when the Mecholyl test is applied). Experimentally-produced states of supranormal sympathetic responsiveness of the hypothalamus are easily reduced to normal levels by drugs such as Pentothal. These and similar drugs or procedures* which reduce hypothalamic sympathetic excitability should be studied systematically in cases belonging to type 1, and the clinical response of the patient should be correlated with the responsiveness to Mecholyl from time to time. Patients of type 2 should not be subjected to physiologic treatments which may alter the autonomic reactivity of the hypothalamus unless other tests show deviations in autonomic responses from the norm.

Valuable as the Mecholyl test may be as an indicator of sympathetic hypothalamic excitability and thereby as a guide for the selection and evaluation of certain types of therapy, it gives only inadequate information about the autonomic state of the hypothalamus. Since parasympathetic and sympathetic functions are exerted by the hypothalamus and since experiments showed clearly how interdependent these functions are, it seems necessary to attempt an evaluation of the state of the parasympathetic excitability and, in conjunction with the Mecholyl test, of the state of the hypothalamic autonomic balance.

The simplicity and sensitivity of the noradrenalin-induced pulse-slowing reflex and the dependence of this reflex on the excitability of the anterior hypothalamus make the noradrenalin test appear to be adequate for this purpose. It will be of fundamental interest to utilize this tool in the service of a physiologically oriented therapy of functional psychoses and other forms of hypothalamic disorders.*

Since this proposed research is virgin territory it would be easy to list a number of problems which should be investigated. The author, however, will not succumb to this temptation, nor will he speculate about the results to be expected. It may suffice to state that these physiologic tests should be used systematically in conjunction with psychologic tests on normal individuals and neuropsychiatric patients and the results should be correlated with the clinical state of the patients under the influence of various forms of therapy. There is little doubt in the author's mind that an extensive program based on a few simple and experimentally proved premises, possibly undertaken on an international scale by a team of physiologists, pharmacologists, psychologists, and clinicians, would go a long way to advance such

*It is interesting to mention that the reduction of the temperature of the body causes a profound loss in sympathetic hypothalamic excitability.[20]

*The intravenous injection of 0.004 to 0.005 mg. noradrenalin is entirely harmless and regularly produces a slowing of the heart rate.

diverse problems as the therapy of functional psychoses, the physiology and psychology of human behavior, the prevention of functional mental diseases, the problem of juvenile delinquency, and many others.

SUMMARY

Experiments on lightly anesthetized cats to determine the relation between hypothalamic functions and the action of certain drugs led to the following results and applications:

1. The action of Mecholyl, acetylcholine, and histamine on the blood pressure depends on the excitability of the posterior sympathetic hypothalamus. If the posterior hypothalamic excitability is increased by the injection of minute quantities of Metrazol or strychnine into this structure, the return of the blood pressure from the hypotenive effect of Mecholyl is accelerated and often followed by a hypertensive phase which is not seen under control conditions. This augmented sympathetic responsiveness is evident also from the fact that other signs of sympathetic reflex responsiveness are increased: they are the acceleration of the heart rate and the contraction of the nictitating membrane which are associated with the return of the blood pressure.

Similar results are obtained if the sympathetic hypothalamic excitability is increased as the result of subthreshold stimulation of the posterior hypothalamus or due to a spontaneous arousal reaction.

If, on the other hand, the posterior hypothalamic excitability is reversibly diminished by the injection of Pentothal or Nembutal into this structure, or if the posterior hypothalamic sympathetic excitability is reduced irreversibly through high frequency lesions in the posterior hypothalamus, the hypotensive drug tests are influenced in the opposite manner: the sympathetic signs which accompany the action of Mecholyl and similar drugs are lessened and the return of the blood pressure from the hypotensive level is delayed or becomes incomplete.

2. The pulse-slowing reflex which is caused by the rise of the blood pressure following intravenous injection of noradrenalin depends on the excitability of the anterior parasympathetic division of the hypothalamus. Reduction of excitability of the area between the optic chiasma and the anterior commissure either by the injection of Nembutal or Pentothal or by high frequency lesions is associated with a distinct diminution of this parasympathetic reflex.

3. The simultaneous application of the sympathetic Mecholyl and the parasympathetic noradrenalin tests in cases with anterior or posterior hypothalamic lesions gives evidence for the fact that the principle of reciprocal innervation regulates hypothalamic functions under physiologic conditions: the posterior hypothalamus holds the anterior hypothalamus in abeyance and vice versa.

4. In the light of these experiments the Mecholyl and the noradrenalin tests may be used respectively as indicators of the sympathetic and parasympathetic excitability of the hypothalamus in the intact human organism. Funkenstein's test reveals that electroshock treatment causes clinical improvement only in patients who show a deficient sympathetic hypothalamic reactivity. At the same time the sympathetic reactivity is restored to normal. On this basis it is suggested that the treatment of functional psychoses be guided by the nature and

degree of autonomic hypothalamic disturbances determined in each patient before and during the period of attempted therapy and be directed toward the restitution of a normal autonomic balance.

5. For full understanding of the mechanism of clinical improvement and the restitution of normal behavior following alterations in hypothalamic functions, it must be taken into consideration that the hypothalamic-cortical discharge has a profound influence on cortical functions underlying sensation, perception, and conditioning and that this discharge is greatly modified (quantitatively and possibly also qualitatively) when the excitability of the hypothalamus is altered.

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Compression of Cervical Portion of the Spinal Cord

Loss of Kinesthetic Sense in the Hands

Luman E. Daniels, M.D.

In view of the small diameter and soft texture of the spinal cord, the many possible differences in effects of compression are rather astounding. Although the history usually suggests a progressive lesion, there is no rule as to the speed of progression. Progression can seemingly come to a halt for protracted periods, and remissions are not unheard of.[1] Pain may persist for long intervals without either loss of function or the appearance of objective neurologic signs. More or less complete transverse arrest of spinal conduction, on the other hand, can develop precipitously, even in cases of benign extramedullary tumor. The fact that conduction may be relatively more impaired in tracts not in the immediate vicinity of the lesion has been a recurring subject for speculation. Departures from the usual train of events appear to be most frequent in intraspinal space-occupying lesions of the thoracolumbar and lumbar regions.[2] They occur fairly often, however, in cases of cervical compression. Craig and Sheldon,[3] in fact, expressed the opinion that bizarre symptoms were most common when the cervical portion of the cord was involved.

In the first case to be presented, there were comparatively few neurologic signs. All but one developed while the patient was under observation, the initial finding being stiffness of the neck. Limitation of spinal motion in the region of compression is especially helpful when the neurologic examination is otherwise unrevealing.[2]

Case 1. A boy aged 13 years was first seen May 22, 1954, a neurologic examination having been advised by a chiropractor. After a fall the preceding winter he experienced pain in his left hip and thigh. He cried at night and finally began to limp. Two and a half months earlier he complained for the first time of aching in the muscles of his shoulders and arms. He had felt so badly the past month that he promptly retired each day on returning home from school. Severe itching caused him to scratch excessively.

It was possible to make a satisfactory examination despite the patient's restlessness and his tendency to run to his mother for comfort. The lad was somewhat obese but nevertheless looked ill. Numerous excoriations bespoke the intense itching he experienced. He held his head inclined to the right and slightly forward. It was practically impossible to force the head

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from this position. Although objective signs were otherwise lacking, there was reason to suspect an intraspinal tumor. The pruritus suggested the possibility of Hodgkin's disease.

The patient was admitted to Children's Hospital for general medical examination and observation. The results of roentgenographic examination of the cervical region were reported as negative. The medical staff seemed most impressed with the mother-fixation, until the concentration of total protein in the spinal fluid was found to be 397 mg. per cent. Since the resident physician neglected to carry out Queckenstedt's test when he performed the lumbar tap, the procedure was repeated May 27, no response to jugular pressure being observed. The fluid contained 655 red blood cells, 1 polymorphonuclear cell, and 10 lymphocytes per cubic millimeter; the protein content was 435 mg. per cent. On this occasion there were a few more neurologic signs. Marked flaccid weakness of the left triceps muscle and moderate weakness of the grip on that side indicated a lesion at the seventh cervical level. Vibratory sensation was slightly reduced in the left leg the following day, and on May 30 the muscles of election were weak in the left lower limb. A day later this weakness was more pronounced and the right lower limb was similarly involved. The left knee jerk was sluggish but on one occasion the ankle jerk was more active on the left. Neither Babinski's reflex nor loss of superficial sensation was demonstrated.

The location of the lesion being fairly certain, myelography was not performed. On June 2 a laminectomy was done and an extradural tumor was removed which was attached to the seventh cervical root on the left side. The original pathologic diagnosis of Ewing's tumor was later changed to lymphosarcoma. Subsequent skeletal survey revealed widespread bony metastases, and closer scrutiny of the original films disclosed minimal rarefaction of the sixth and seventh cervical vertebrae. Roentgen treatment was given and the patient felt much better when he left the hospital. He experienced severe convulsions in September of the same year and died the following November.

Muscular weakness was first noted in the left upper extremity in the first case and was apparently due to pressure on the seventh cervical nerve root. Symptoms and signs of radicular involvement are rather common in cases of protruded intervertebral disk in the cervical region, even when cases of lateral herniation are excluded.[4,5] The studies of Craig and Sheldon[3] indicated that weakness came on first in the upper extremities in a little over half the cases of tumors in the cervical region. As will be shown subsequently, the rule also applies when the growth lies too high to affect directly the lower motor neurons innervating the muscles of the upper extremities.

Case 2. A Greek man aged nearly 72 years was examined in St. Joseph's Hospital December 17, 1954. Beginning one year before, he had experienced numbness, first in his hands and then in his entire body below the neck. His hands had been weak for some time and he had been unable to walk the past three weeks. He did not complain of pain. Physicians who attended him previously were said to have considered his difficulties functional in nature.

Examination revealed a poorly nourished and apathetic elderly male. Because of poor cooperation, it was difficult to work out a motor pattern. Weakness in the upper extremities seemed to be most marked in the hands; the flexors of the hips and knees were the muscles mainly involved in the lower limbs. Sensation for pain and temperature was diminished to the upper limit of the second thoracic segmental zone. Appreciation of pinprick was somewhat impaired well into the fifth cervical segmental area. Vibratory sensation appeared to be abolished below the clavicles and the manubrium of the sternum. Positional sense was decidedly reduced in the fingers and moderately reduced in the toes. Ataxia was correspondingly more pronounced in the upper extremities. The tendon reflexes were only a trifle hyperactive, although Babinski's reflex and a few strokes of ankle clonus were elicited. The dynamics of the spinal fluid were interesting. With the head flexed, there was a prompt response to jugular compression; when the head was held straight or extended, there was no response. The concentration of protein was 108 mg. per cent. Roentgenographic examination revealed marked narrowing of the fifth

cervical intervertebral space, with pronounced hypertrophic lipping anteriorly of the contiguous vertebral bodies. The fourth cervical intervertebral space was narrowed posteriorly and there was some posterior lipping of the fourth, fifth, and sixth cervical vertebrae.

Myelography revealed a large defect at the fifth and sixth cervical levels, the defect being most pronounced at the fifth. Laminectomy disclosed a protrusion of the fifth cervical intervertebral disk large enough to cause posterior bowing of the cord. A smaller protrusion was found a segment higher. Since the protrusions were bony hard and anterior to the cord, the surgical procedure was limited to section of the dentate ligaments and decompressive laminectomy. Use of the hands subsequently improved and the patient was able to walk when he cared to make the effort. He succumbed to massive myocardial infarction June 19, 1955.

The effects of compression of the cervical cord by disk protrusion vary widely. MacDonald[6] and his associates reported a case in which there was a modified Brown-Séquard syndrome, with sensory loss predominating over motor impairment. Sometimes there are no significant sensory changes. Atrophy and fasciculation in the muscles of the upper extremities associated with spastic weakness of the lower limbs may simulate amyotrophic lateral sclerosis. Appreciation of passive motion was reduced in the fingers in 14 out of 45 cases of cervical spondylosis with neurologic complications studied by Brain and his associates.[4] It was much less common, on the other hand, in a series of 32 cases of midline cervical disk protrusion reported from the University of Chicago clinics.[5] To avoid possible confusion, it should be stated parenthetically that in choosing a title British authors emphasize osseous changes.[7] American writers on the same subject seem more preoccupied with posterior bulging of the disk. Although degeneration of the intervertebral disk is believed to be the primary change, the sharp transverse ridges of bone which ultimately develop also help to indent the anterior surface of the cord.

Despite the roentgenologic findings in case 2, marked loss of proprioceptive sensation suggested the possibility of a tumor lying posterior to the cord. With this case fresh in mind, another patient was seen with incoordination of his upper extremities due to loss of positional sense. The roentgenographic films looked normal enough, but the mode of onset and the irregular course aroused the fear that this might be another case of protruded disk. There was sufficient indication of the Brown-Séquard syndrome, however, to suggest a tumor involving the cord on the right side. It is interesting to note that, although the left lower limb had felt cold for five years, superficial sensation was impaired no higher than the upper part of the thigh. The only other constant symptom until a year before was faulty control of the right hand. Respiratory difficulties apparently came on early but were fortunately intermittent and never reached serious proportions.

Case 3. A chiropodist aged 51 years was examined February 18, 1955. While heaving a hod of coal seven years before, he felt something crunch in the lower cervical region. For the next week he could hardly turn his head and the pain was so severe that he often slept sitting in a chair. The pain later subsided but recurred whenever he contracted a cold and coughed frequently. On one occasion a hard cough brought on severe pain and weakness in the right shoulder which persisted for a month. The following winter he experienced flashes of heat in the left lower limb, which a year thereafter began to feel cold. He later experienced spells of dyspnea. During one of these attacks two years before, his abdomen felt numb and the diaphragm did not seem to be working properly. Use of the right hand had been impaired the past two or three years

and consequently the patient had trained himself to use his left hand. The gait had been unsteady the past year. During a bout of influenza three weeks before, coughing provoked pain in the back of his neck and it had since been difficult for him to raise his arms. He was no longer able to manipulate the fingers of his right hand and the left hand was becoming numb and unmanageable.

Examination revealed pronounced weakness of the abductors and external rotators of the arms and the flexors of the forearms. The grip was weak, more so on the right side. Fascicular twitching was noted in the right biceps brachii muscle but there was no muscular atrophy. The lower limbs were normally strong. Positional sense in the fingers was markedly reduced on the right and moderately diminished on the left. When the toes were tested, a slight hesitancy in the patient's replies was the only indication of disturbed postural sense. Vibratory sensibility was abolished in all four extremities. Sensation for pinprick was diminished in the left lower limb as high as the upper part of the thigh. The tendon reflexes were more active on the right and Babinski's reflex was elicited bilaterally. The arms and legs, particularly the right arm, were ataxic.

On March 10 Queckenstedt's test revealed a partial block, and myelography disclosed a space-occupying lesion extending from the second to the fourth cervical vertebra. The concentration of protein in the spinal fluid was 147 mg. per cent. A meningioma with a dural attachment anterolateral and to the right of the spinal cord was removed on March 14. Recovery of function was gratifying and uneventful.

The spinal cord was compressed at a midcervical level in case 2 and somewhat higher in case 3. In cases of compression in the region of the foramen magnum, weakness and numbness are first experienced, as a rule, in the upper extremity on the side of the lesion. Positional sense may be markedly impaired either in the hand on the side of the lesion or in both hands and yet be affected little if at all in the feet. The careful observations of Symonds and Meadows[8] are especially instructive in this respect. They found articular sense completely lost in the fingers in a case of neurofibroma lying anterior to the cord, and in all joints of the upper extremities in a case of meningioma situated anterolaterally. Postural sensibility was intact, however, in a case of meningioma lateral to the cord; it was barely affected in the fingers on the side of the lesion and normal elsewhere in another with a posterolateral location. Craig and Sheldon[3] mentioned the case of "a large meningioma presenting exactly in the midline posteriorly" in which joint and vibratory sensibilities were not altered. Boshes and Padberg[9] found appreciation of passive motion profoundly affected in one or both upper extremities in high cervical lesions of various types. These authors stressed the importance of stereoanesthesia which might be present when graphesthesia, or the ability to recognize numbers written on the skin, was not impaired. Inability to recognize objects by the sense of touch is an early complaint in some cases of cervical compression. Stereoanesthesia due to loss of sensation is frequently confused with astereognosis, and when present in only one hand has led to the erroneous diagnosis of a parietal lesion. In their review of 74 cases of tumor of the foramen magnum, Love and his associates[10] reported decided reduction or loss of joint sense in 19 cases without going into further detail. They stated, however, that astereognosis was noted in 18 cases, in 12 of which it was bilateral. Astereognosis was accompanied by sensory disturbances in 16 of the 18 cases. Loss of kinesthetic sense in the left hand was an outstanding symptom in a personal case of craniospinal meningioma. The growth was attached anterolateral to the medulla oblongata and compressed both

the bulb and the first cervical segment on the left side.

In compression of the thoracic cord, marked loss of vibratory sensation with minimal loss of positional sense is frequently associated with a tumor lying posteriorly. Meningiomas posterior or posterolateral to the cord, however, are common in this region of the spine. Kahn[11] suggested that, in cases of anterior compression, anchoring of the cord by the dentate ligaments prevented the posterior columns from being pressed against the bony laminae. Observations in a recent case of midline disk protrusion indicate that this protection is not absolute, even at a thoracic level. In the cervical region the posterior columns, notably the fasciculus cuneatus or Burdach's tract, seem to be protected still less. The lateral funiculus was in proximity to the tumor in case 3, yet conduction was more impaired in Burdach's tract than in either the spinothalamic or the pyramidal tracts. In the cervical segments, Burdach's tract tends to dwarf the fasciculus gracilis of Gall. There must be a large contingent of proprioceptive fibers coming from the upper extremities to provide for coordination of the intricate movements of the hand.

The relatively free range of motion in the cervical portion of the spine and the frequent movements of the head in the course of an individual's daily life have also to be considered. By means of myelographic studies on cadavers, Taylor[12] showed that hyperextension of the head exerted pressure on the cord by an infolding of the ligamenta flava. He pointed out that fixed protrusions anterior to the cord acted as counterpoints to the pressure of the forward bulging ligamenta flava. Taylor's paper and one written by Schneider and his associates[13] dealt with acute hyperextension injuries. It would seem, nevertheless, that with a cord already seriously compromised by either a tumor or a protruding disk, extension movements of less range and much less force could have a damaging effect on the posterior columns. Because of its bulk and lateral position, Burdach's tract should be encroached upon to a greater degree than Gall's tract. Manometric observations in case 2 indicated that there was more room for the cord with the head flexed than with it either straight or extended.

Not the least interesting feature in some cases of tumor in the region of the foramen magnum is the paucity of clinical findings. The neurologic symptoms and signs may be limited to pain in the neck and occiput and tightness of the cervical muscles. There were no sensory or motor symptoms in 15 of the 74 cases studied by Love and his associates.[10] Stookey[14] pointed out that the uppermost cervical segments and the portion of the bulb within the foramen magnum lie in a large basal cistern. Growths in this region can consequently reach considerable proportions before interfering with conduction in the long tracts. Another source of protection is splinting of the neck muscles. It may be of some significance that there are no ligamenta flava above the second cervical vertebra; they are replaced there by the posterior atlantooccipital membrane and thin sheets of fibrous tissue stretched between the laminae of the atlas and axis.[15]

SUMMARY

Three cases illustrative of the varying clinical picture associated with cervical cord compression have been reported.

In a case of extradural lymphosarcoma, stiffness of the neck was the only objective sign when the patient was first seen. Protrusion of the fourth and fifth cervical intervertebral disks was the source of compression in the second case, and a tumor at the third and fourth cervical levels in the third. Loss of positional sense in the hands was the outstanding feature in the last two cases. Different mechanical factors were considered.

CONCLUSIONS

1. It is possible at times to make a diagnosis of compression of the spinal cord when there are relatively few objective findings.

2. When the spinal cord is compressed at a midcervical or higher level, kinesthetic sense may be more impaired in the upper than in the lower extremities.

3. The posterior columns, notably the fasciculus cuneatus, are not too well protected in cases of either anterior or anterolateral compression.

4. Whenever proper control of one or both upper extremities is lost owing to impairment of postural sensibility, the possibility of a lesion involving the cervical portion of the spinal cord should be seriously considered.

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Pallidum and Muscle Tone

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INCREASE OF MUSCLE TONE without increase of the tendon reflexes in diseases of the globus pallidus is regarded as one of the most certain facts in the pathology of the extrapyramidal system. As a result the expression pallidal rigor has been widely accepted. In a number of diseases associated with more or less extensive destruction of the pallidum, such as carbon monoxide poisoning or Wilson's disease, the resistance of the skeletal muscles against passive distension is increased. This experience has led to the concept that the pallidum has an inhibitory effect upon lower tonus maintaining reflex arcs or that the increased activity of these reflex arcs in pallidal diseases is a release phenomenon due to elimination of efferent impulses from this ganglion.

Under the influence of this concept, we have restricted ourselves to production of rather small lesions in order to avoid as far as possible an undesirable increase of muscle tonus when producing stereotaxic lesions in the pallidum (pallidotomy[1]) or in the ansa lenticularis (ansotomy[2]) for the relief of involuntary movements or tremor. Surprisingly, in none of the 25 cases studied so far have such circumscribed lesions of the pallidum or of the ansa lenticularis induced an increase of muscle tone. In some instances there was even a decrease of the rigidity.

It seemed desirable to base these results not only upon gross clinical impressions, but as far as possible upon objective recordings. Consequently, a myotonograph was built in which the extremity under study was examined with the axis of the respective joint in a vertical position, as in a previously devised apparatus.[3] A spring dynamometer similar to that used by Schaltenbrand[4] is part of the apparatus.

METHOD

The myotonograph (figure 1) consists of a motor driven basic arm *A* that rotates about a vertical axis, and a measuring bar *B* that is mounted above *A* and rotates about the same axis but is independently pivoted. *B* carries on either side, at a right angle to it, springs *S'* and *S''* that serve as dynamometers and are connected to *A* by a transverse bar *T'*. If the extremity fixed to *B* offers a resistance to the passive movement transmitted by *A*, *B* tends to deviate in relation to *A* in a direction opposite to the passive movement and the spring

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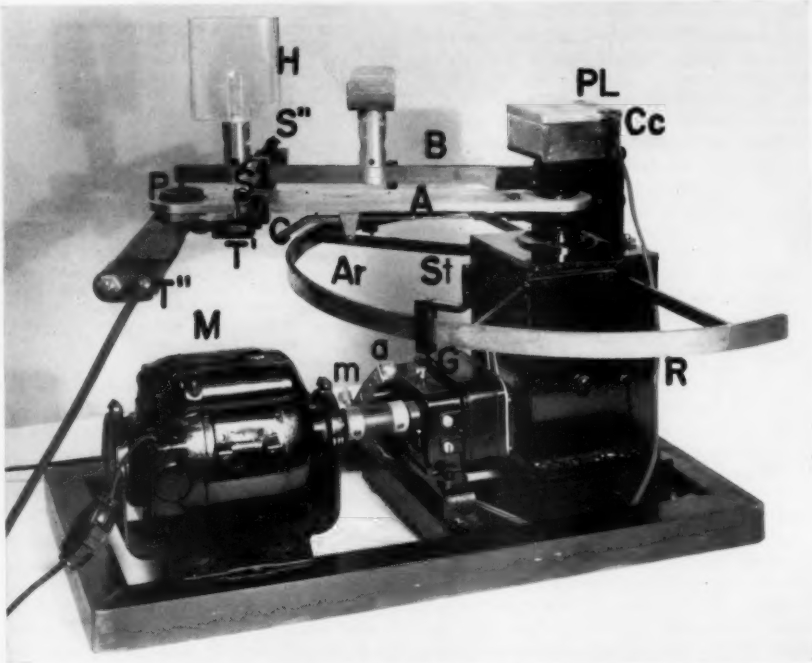

FIG. 1. Myotonograph. *A* basic arm, *a* arm of the Zero-Max torque converter, *Ar* arc, *B* measuring bar, *C* clutch, *Cc* contains circular contacting device, *G* gear reducer (Zero-Max torque converter), *H* hand-rest (for testing the elbow), *M* motor, *m* mercury switch, *P* pin, *Pl* plastic plate, *R* right angle gear reduction unit, *S'*, *S"* dynamometer springs, *St* stop, *T'* transverse bar, *T"* transverse bar holding on its undersurface the pneumograph bellows (latter not visible in the photograph).

resisting the movement of *B* is distended. The distension of the spring and the resultant displacement of *B* against *A* give a measure of the resistance offered to the passive movement and thus indirectly of the muscle tone. The measuring bar *B* is connected by a pin *P* to one end of a Manning pneumograph bellows; the other end of this bellows is fixed to *A* by a transverse plate *T"*. When the measuring bar *B* is displaced from its resting position, the pneumograph bellows is stretched or compressed and the resultant changes of intratubal pressure can be recorded. We used for this purpose the pneumographic recorder of a Stoelting Deceptograph. A variable air leak connected in parallel to the pneumograph bellows acts as a variable damper.

The dynamometers may be varied by using springs of various wire size and diameter, and/or by changing the position of *T'* and thus the distance between the axis of the apparatus and the point of attachment of the springs and by varying the extension of the springs.

The basic arm *A*, as mentioned above, is motor driven. The motive train consists of an electric motor *M* (¼ h.p.), connected to an infinitely variable gear reducer *G* (Zero-Max torque converter) equipped with reverse. This in turn is connected to a right-angle gear reduction unit *R* which drives the arm *A* through a clutch *C*. This clutch is arranged in such a manner that the motive power is disengaged when the arm comes to the end of a predetermined arc of travel. The actual travel of the arm can be easily set by means of stops *St* placed on the large arc *Ar*.

In actual use, the extremity (forearm, hand, or lower leg) is strapped to the measuring bar *B* in such a manner that the axis of the joint under study is directly above the axis of the apparatus. The variable stops are set and the clutch on the basic arm is locked. As long as the arm *a* of the torque converter is set at neutral, no motion takes place.

When everything is ready, the arm *a* of the torque converter is engaged. At the same time, by means of a mercury switch *m* attached to this arm, the electrical circuit indicating the travel of the basic bar is actuated. This circuit is closed at each 15° by a circular contacting device (contained in *Cc*) so that for each 15° of travel of the basic arm, a pip is registered by the recording galvanometer of the Stoelting Deceptograph on the same record as the tonographic tracing.

The device is calibrated by recording the displacement of *B* against known weights. The minimum measurable force seems to be in the neighborhood of 100 gm. and the maximum several kilos.

The graphs obtained with this apparatus (figures 2 to 5) represent the resistance of an extremity to passive movements (ordinates) in relation to the range of the flexor or extensor movements (abscissas). Since the distances of the vertical lines printed on the recording paper indicate time intervals, the records show also the speed of the passive movement.

It is evident that the passive resistance recorded in these graphs depends not only upon the innervation maintaining the muscle tone but also upon the physical properties of the muscles and of other soft tissues, on the weight and the inertia of the extremity, the friction of parts of the apparatus between the bar *B* and the extremity, also on possible vibrations of the springs. Therefore, we cannot obtain from these curves absolute values of the muscle tension but only comparative values. If all other factors remain identical, graphs obtained before and after a therapeutic procedure (administration of a drug, operation) under otherwise identical conditions may show us changes of muscle tension induced by such a procedure.

If one performs such recordings, two particular sources of error have to be guarded against: 1) The first is friction between the extremity and bar *B* caused by longitudinal movements of the extremity on *B* during the passive flexor or extensor movements. This occurs when the axis of the extremity and that of the apparatus do not coincide. In order to facilitate a correct positioning of the axis of the extremity, the position of the axis of the apparatus is marked on a plastic plate *Pl* on top of the apparatus. Furthermore, it is advisable, before driving *A* by means of the motor, to perform manually passive movements of *A* and to correct the position of the extremity until no movements of the extremity on *B* in the longitudinal direction are noticeable. 2) A second source of error are voluntary innervations performed by the subject that may either offer an active resistance to the passive movements or may perform active movements in the direction of the passive movements. In order to eliminate this factor, one has not only to instruct the subject to relax and to pay no attention to the movements of the extremity, but one has also to try to divert the subject's attention from the passive movements as much as possible. In some cases it may be advisable to perform the measurements during sleep or under hypnosis.

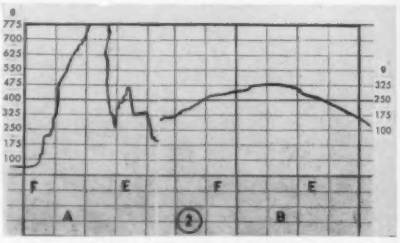

FIG. 2. Spastic paraplegia. Resistance to passive movements on 60° flexion (*F*) and extension (*E*) of the knee before (*A*) and 30 minutes after (*B*) injection of Intracaine in the respective muscles. Ordinates: Resistances in grams. Time intervals (distances between vertical lines) = 5 sec.

The usefulness of the apparatus for testing the effect of changes of the static innervation upon the resistance of the skeletal muscles to distentions is shown in figure 2, in a 23 month old child who developed a severe spastic diplegia following birth anoxia. Intracaine in oil 4 cc. were injected, (1 cc. in the lateral hamstring, 1 cc. in the medial hamstring, 1 cc. in the adductors, 1 cc. in the gastrocnemius). One notices a steep rise of the graph recording the resistance of the flexors and extensors of the knee before the injection and a definite

flattening of the curve and a lowering of its height 30 minutes following it. In other words, there is a definite decrease in the muscle tone as a consequence of paralysis of the proprioceptor nerves demonstrable in these records.

RESULTS

Myographic recordings confirm the clinical impression obtained on performance of passive movements that the resistance of the skeletal muscles against distention is not increased by circumscribed lesions of the ansa lenticularis and may even be diminished in some instances. Figures 3 and 4 show flexion-extension records from the left elbow of a patient suffering from parkinsonism before and one week after right-sided ansotomy. It can be noted that the resistance against passive movements on flexion as well as on extension is reduced by about one half. In figure 5 the tremor has been recorded so that the midpoint of the tremor oscillations must be used as a measure of the distention resistance. A comparison of the graphs before (*A*) and some weeks after (*B*) the operation shows that the tremor as well as the resistance to passive movements are decreased. It should be emphasized that these patients did not show any signs of pyramidal tract involvement such as Hoffman or Babinski phenomena. The dynamometric readings in some instances showed a slight decrease in the initial period after the operation which was only transitory; also, with the reappearance of the preoperative values of the dynamometric readings, rigor did not appear.

The absence of development of rigidity could also be corroborated by measurement of the frequency of alternating

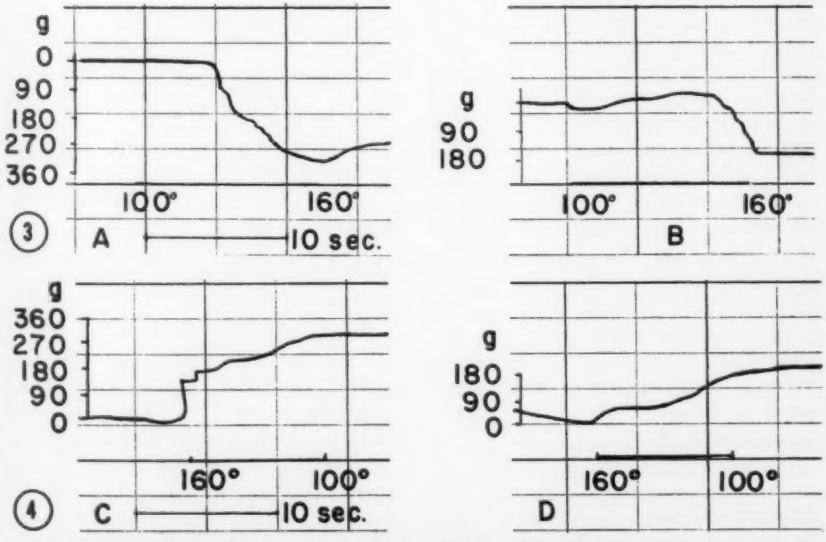

FIG. 3. Paralysis agitans in a 42 year old female. Passive flexion of the left elbow before (*A*) and one week after (*B*) lesion of the right ansa lentiformis. Ordinates: resistances in grams.

FIG. 4. Same patient. Passive extension of the left elbow before (*C*) and one week (*D*) after lesion of the right ansa lentiformis.

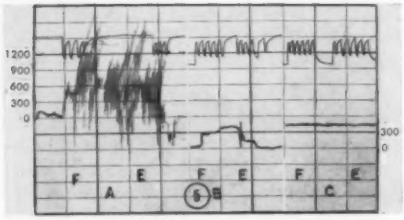

FIG. 5. Postencephalitic parkinsonism in a 32 year old man. Resistance to passive movements on flexion (*F*) and extension (*E*) of the elbow before (*A*) and after (*B*) lesion of the ansa lentiformis. *C* corresponding record from the normal arm. Uppermost graph: Each spike indicates a rotation by 15°. Time intervals (distances between vertical lines) = 5 sec. Ordinates: resistances in grams.

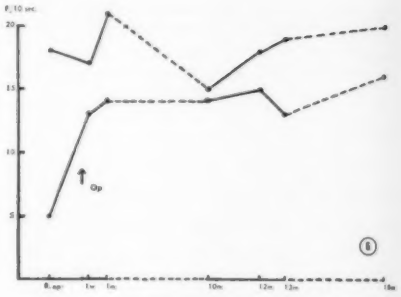

FIG. 6. Paralysis agitans (same patient as in figures 3 and 4). Frequencies (per 10 sec.) of alternating flexor-extensor movements of the fingers before and after ansotomy. *B. op.* before operation, *L* left side, *m* month, *R* right side, *w* week.

flexor-extensor movements of the fingers. Before operation these patients frequently show a bradykinesis. In many instances this was improved following ansotomy so that a definitely higher frequency of the alternating flexor-extensor movements of the fingers was obtained than before operation (figure 6). This improvement of the frequency of such alternating movements could be observed also in patients who showed no definite pathologic increase of tone before operation and probably is only partly caused by a diminution of the resistance of antagonistic muscles. Although the factors that cause this improvement of alternating movements are only poorly understood at present, these findings indicate that the lesion of the ansa does not induce an increase of resistance of the muscles to distention, which would result in increase but not decrease of the bradykinesis.

We have histopathologic findings only in one case, a woman suffering from Huntington's chorea who died following an accident over one year after bilateral pallidotomy. In addition to atrophy of the caudate nuclei, histologic studies revealed small electrolytic lesions in the inner segments of the anterior part of the pallida at the level of the transverse fibers of the anterior commissure. The right-sided lesion encroached upon the ventral part of the anterior limb of the internal capsule. The corticofugal fibers to the extremities were not affected, since Weigert preparations of the medulla oblongata showed that both pyramidal tracts were intact.

In the other cases the position of the lesion can only be estimated according to the operative coordinates and the postoperative studies of Pantopaque droplets injected at the site of the electrolysis (figure 7). From these data it may be inferred that the ansotomy was performed at the level of the anterior commissure and 3 to 6 mm., in some instances even 9 mm., behind it when the observation of the tremor during operation indicated the necessity of extending the lesion into posterior levels. The ventral part of the pallidum was also affected by the lesion so that we deal with a combined pallido-ansotomy.

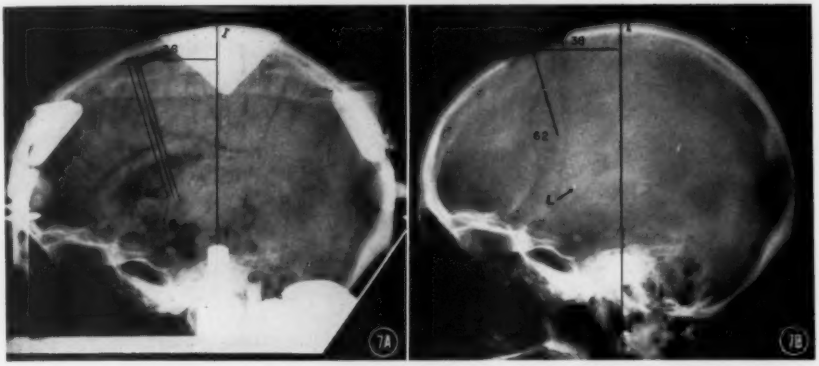

FIG. 7. Lateral roentgenograms of the patient represented in figures 3, 4, and 6. *A.* Preoperative roentgenogram showing three planned punctures. One reaches the anterior commissure; the two others are 3 and 6 mm. posterior. The most anterior puncture enters the brain 38 mm. anterior to the interaural line (*I-I*) and reaches the anterior commissure at a depth of 62 mm. *B.* Postoperative roentgenogram showing trace of puncture at 38 mm. anterior to interaural line (*I-I*) and area of electrolysis (*L*) 62 mm. deep.

The question arises as to how one may explain the difference between these findings and the observation that pathologic processes in the pallidum induce a rigor of the skeletal muscles. One may surmise that the duration of the pathologic process plays a role. Therefore, it should be emphasized that in those cases which we were able to observe from two to three years following ansotomy, no signs of development of rigidity were noticed. Furthermore, the possibility may be considered that some pathologic processes induce a gradual destruction of the cells of the pallidum, while in these operations we deal with a sudden elimination of pallidal impulses. The possible importance of this factor should not be denied; however, it should not be overestimated, since carbon monoxide intoxication which also produces an acute lesion of the pallidum may be followed by the development of rigor.

Differences in the extent of the lesions seem to be of greater importance in our problem. In this material one deals with circumscribed partial lesions of the pallidum affecting the ventral part of this ganglion and the efferent fibers lying on its ventral periphery, while the dorsal part and probably the majority of the fibrae perforantes are spared. In contrast, the pathologic processes usually observed in the pallidum, such as carbon monoxide poisoning, kernicterus, Wilson's disease, Hallervorden-Spatz's disease, and Van Bogaert's progressive pallidal atrophy, are diffuse processes usually affecting large parts of the ganglion and in many instances also the substantia nigra (Hallervorden-Spatz's disease), the putamen, and the cerebellum (hepatolenticular degeneration, carbon monoxide poisoning). It is also interesting to note that, following ligature of the anterior choroidal artery,[5] rigor failed to develop or became reduced. However, in view of the variability of the area supplied by this artery, it seems hardly possible to decide to what extent the pallidum and to what extent lower parts of the extrapyramidal system are

affected by this operation. In a patient in whom one anterior choroidal artery had previously been ligated, electrography of the corresponding pallidum by depth electrodes showed a regular 9 to 10 per second rhythm, so that it can hardly be assumed that in this instance the ligature had interfered with the pallidal activity.

Circumscribed lesions of the ventral part of the pallidum and of the efferent fibers contained in the ansa lenticularis do not produce an increase in tone and in some instances even diminish the rigidity, while diffuse pallidal disease results in rigidity. This suggests that, besides the efferent fibers which inhibit the tonus-maintaining reflex arcs, there are also efferent fibers that have a facilitating action upon these reflexes. The effect of ansotomy seems to suggest that such facilitating impulses are conducted chiefly by fibers of the ansa lenticularis, while in diffuse diseases the loss of pallidal inhibition dominates the picture, so that release phenomena of the lower reflex arcs develop and induce a rigor. The affection of extrapallidal neurons may also play a part. This explanation should be considered as a working hypothesis only, and further studies testing its validity are planned.

SUMMARY

1. In contrast to the rigor induced by diffuse diseases of the pallidum, circumscribed lesions of the ansa lentiformis and of the adjoining part of the pallidum are not followed by increase of muscle tone; in some instances even a reduction of the rigor can be observed in patients suffering from paralysis agitans or postencephalitic parkinsonism.

2. These observations are substantiated by recordings of the resistance to passive movements by means of a specially devised myotonograph.

3. The diminution of the bradykinesis following ansotomy in patients suffering from postencephalitic parkinsonism or paralysis agitans is in agreement with these findings; however, bradykinesis may also be favorably influenced in the absence of rigor.

4. A working hypothesis is offered suggesting that the various efferent fibers of the pallidum are functionally not equivalent; besides tonus inhibiting fibers, there seem to exist, particularly in the ansa lentiformis, pallidofugal fibers that conduct facilitating impulses to lower tonus maintaining reflex arcs.

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Petit Mal Status

Epilepsia Minoris Continua

Walter J. Friedlander, M.D. and George H. Feinstein, M.D.

ACCORDING TO GIBBS[1] episodes of petit mal status are found in 3 per cent of patients with petit mal epilepsy. Bridge[2] reported only nine children who had episodes of petit mal status in his large series, which represents 2.2 per cent of all children who had "minor seizures" but 10.8 per cent of those who had "petit mal." A review of the literature also reveals that the condition is quite uncommon; it is not described in most of the standard neurology textbooks, except by Jelliffe and White.[3] Lennox[4] states that it is rare.

Its rarity is not its only interesting aspect. Because of the patient's bizarre appearance for hours or days, it may be easily mistaken for an acute psychiatric disorder. Hence, since recognition of a petit mal status may be difficult and also because descriptions of the condition are rare, the report of a rather unique case and a review of the literature concerning this disorder appears worthwhile.

CASE REPORT

A 30 year old, white, rather obese married housewife was first seen in the neurology clinic on March 20, 1954 complaining of episodes of inability to think clearly for periods of one to two days. The first episode occurred 14 years earlier, shortly after she had visited her grandmother for the first time on a locked psychiatric ward, and since that time they have occurred about once every three to five months, usually right after awakening in the morning. She described difficulty in thinking during these times but said she was able to carry on some normal activity and could comprehend and reply to what was said to her. She can make breakfast for her husband and child during such an attack, but after they are taken care of she returns to bed and remains there. The episodes begin and end abruptly. The mother states that the patient appears dazed during these spells, answers questions slowly and incompletely, and has a "palpitation" above her eyes.

There was no history of any other episodic disorder, such as loss of consciousness, convulsions, or momentary blank spells. The patient was second in birth order and there was no history of any birth trauma. There have been no febrile convulsions or "spasms;" the only history of trauma was a rather minor injury at the age of three years, at which time she fell and struck her right temple but did not lose consciousness. There have been no remarkable diseases except otitis media at the age of six or seven months. The mother believes that there may have been some personality change following this although she could not be any more specific. As a child she developed somewhat slowly and did not talk until the age of five.

An older brother had grand mal convulsions between the age of 16 and 20 which were

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believed due to a serious head injury. In no other members of the family was there anything to suggest epilepsy. The only other possible contributing factor in the family history is the fact that the patient's grandmother died "insane" at the age of 80.

Neurologic and physical examinations at the time of her first clinic visit and subsequent examinations were negative. The patient had sought medical attention at another clinic in June 1949 where essentially the same history and physical and neurologic findings were obtained. An electroencephalogram made August 4, 1949 was interpreted as showing ". . . no clear signs of focal change. The record is compatible with a slight generalized cerebral dysfunction of convulsive . . . type." She was placed on Dilantin 0.3 gm. and phenobarbital 0.45 gm. a day but this did not change the frequency of her episodes.

An electroencephalogram obtained at this hospital on April 29, 1954 showed a basic record of 8 cps. with some superimposed 6 to 7 per second activity and a small amount of sharp wave activity. The conclusion was that this was a mildly abnormal record consistent with, but not diagnostic of, an epilepsy. A repeat record obtained on May 13, 1954 was essentially the same.

In light of the onset and description of the attacks, it was felt that these episodes were probably not epileptic seizures. However, the patient and her mother were asked to return to the clinic during an episode so that she could be observed. An attack began the morning of July 5, 1954 and she reported to the hospital. When first seen she was walking about normally; she recognized her physician and smiled appropriately as he approached. She said that she was feeling all right, and readily followed directions about going into the examining room and seating herself. During the first minute or so of the examination nothing unusual in her manner was noted, but as she was questioned further it became apparent that there was slowness in comprehending certain questions, particularly those having to do with dates and numbers. Occasionally she answered only after a short pause and sometimes did not give a complete answer. The neurologic examination was again negative except for a constant tremor of both eyelids and a twitching of the eyebrows; no other involuntary movements were noted. An electroencephalogram was obtained immediately and showed constant 3 to 4 per second spike-wave complexes in all leads (figure 1). A repeat record obtained approximately four hours later revealed the same pattern. The patient replied to questions and was able to count serially while the spike-wave complexes continued to appear in the electroencephalogram. By the use of a previously described apparatus modified for this purpose,[5] the movements of the eyelids were recorded simultaneously with the electroencephalogram; the lid movements were synchronous with the spike-wave compelxes (figure 2).

Because of this episode the patient was hospitalized. Laboratory studies revealed normal hemogram and urinalysis. Lumbar puncture was normal except for 68 mg. per cent total protein. Serum calcium was 12 mg. per cent; the urinary Sulkowitz test was negative. A glucose tolerance curve revealed a mild diabetic curve, with only a trace of glucose in the urine in the one hour sample. Chest and skull roentgenograms were normal. The electroencephalogram was repeated on July 6 and again showed 3 to 4 per second spike-wave complexes; though these were almost constant, there were more "free periods" than noted before. During this time she continued in essentially the same mental state, was able to recount various things that had occurred in the immediate past; the twitching of the eyelids and eyebrows persisted.

Before she was seen on the morning of July 7, the intern who had seen her earlier reported that she thought she was about the same. Actually, the seizure had ended; the eyelid twitching had stopped and she appeared to be as alert as she was in her preictal state. This observation is of some interest in that it indicates the lack of any marked intellectual impairment during her seizure.

An electroencephalogram done on July 7 showed essentially the same pattern as obtained in her preictal state (figure 3). Subsequently, the blood calcium, glucose tolerance, and spinal fluid studies were repeated and revealed that the calcium was 11 mg. per cent, the glucose tolerance curve was essentially the same as before, and the spinal fluid protein was now normal. On September 22 a pneumoencephalogram showed nothing remarkable. An electroencephalogram obtained on September 21 was the same as the pre- and postictal records. Medication was adjusted to phenobarbital 0.03 gm. and Tridione 0.3 gm. once

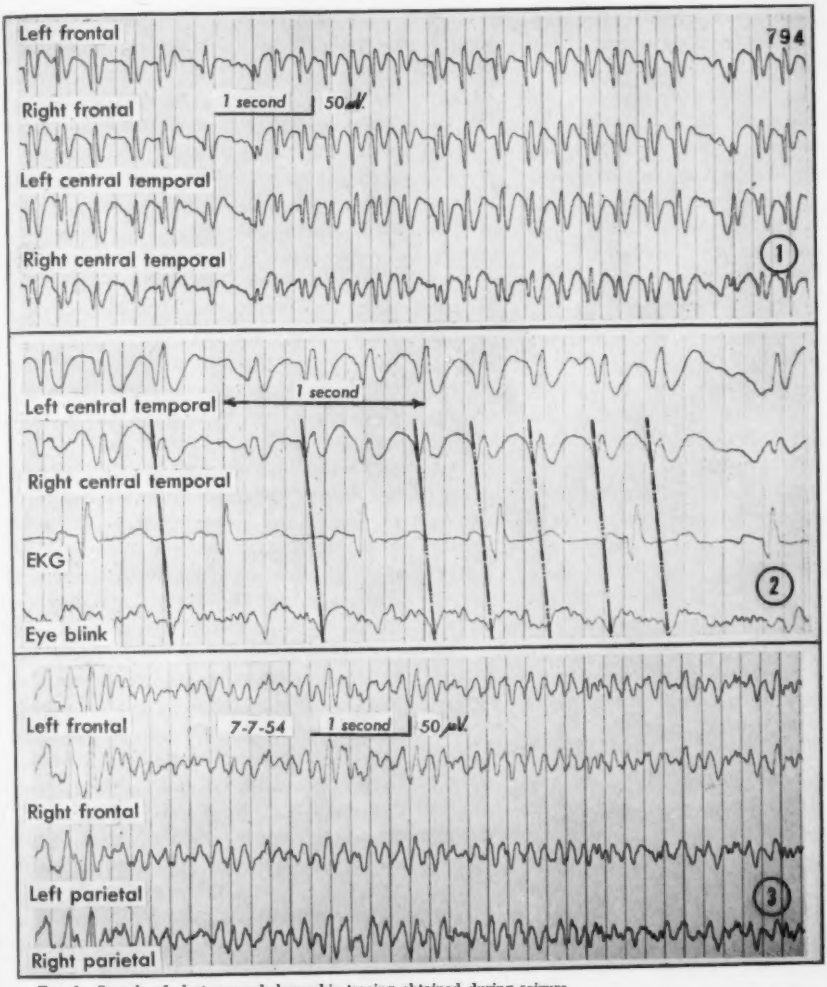

FIG. 1. Sample of electroencephalographic tracing obtained during seizure.
FIG. 2. Simultaneous electroencephalogram and recording of eye blink showing synchrony between spike-wave complexes and eye-lid movement.
FIG. 3. Sample of tracing obtained during seizure-free period.

a day and she has remained free of seizures for over a year.

REVIEW OF LITERATURE

Putnam and Merritt[6] described ten patients who had "dullness" which was felt to be an "epileptic equivalent." One of their patients was a 32 year old man who had had grand mal seizures since the age of six, as well as other episodes during which time he found himself dull

and lacking in initiative even though he was conscious, oriented, and mentally stable; these episodes lasted several days. An electroencephalogram obtained during such a "dull" period revealed the presence of spike-wave complexes, a finding which was not seen during a seizure-free period.

Tucker and Forster[7] reported two cases of petit mal status. The first one was a 43 year old woman who had both petit mal and grand mal seizures. Her generalized seizures were preceded by a feeling of confusion which lasted for several days. The patient became confused three days after a mastectomy was performed. There were no myoclonic movements. The differential diagnosis was: 1) reactive depression precipitated by suspicion of carcinoma, 2) psychomotor seizures, 3) petit mal status of a short stare type, and 4) dreamy state secondary to a lesion of the temporal lobe, perhaps a metastatic carcinoma. An electroencephalogram revealed "bilaterally synchronous 3 per second wave and spike formations occurring in long bursts and occupying 17 of the 20 minutes employed in the tracing." The entire episode lasted 36 hours. Their second case was a 14 year old boy who also had petit mal and grand mal seizures as well as "psychomotor-like" episodes during which there were "several minutes to hours of confusion, disrobing, irrelevant production, and walking around with a peculiar steppage gait." He had myoclonic movements of the extremities during at least some of these spells; an electroencephalogram during such an episode showed "bilateral 3 per second spike waves occurring in long runs with only short intervening bursts of normal electrical activity."

An eight and a half year old girl with congenital brain damage, mental deterioration, "head nodding and falling attacks, myoclonic jerks, and frequent convulsions" has been described by Lennox and Davis;[8] an electroencephalogram obtained while the girl was having a spell contained 2 per second spike wave complexes with a temporal focus. Cossa and Martin[9] described a rather prolonged episode of automatism in a patient with petit mal during which time there were spike wave complexes in the electroencephalogram. In Bridge's[2] report of nine children who had petit mal status, two cases are described in detail. Both had a history of petit mal seizures and at least one of these patients had flickering movements of the eyelids, trembling, and rhythmic movements of the hands and arms during the episodes of status. He commented that "because of the picture of semiconsciousness and confusion that the patient exhibits, the diagnosis is sometimes confused with epileptic equivalent, psychotic states, or sudden mental deterioration." He felt that the status followed an increasing number of single petit mal attacks; no one else has noted this phenomenon.

More recently Vizoli and Magliocco[10] described a 20 year old man who had petit mal seizures, some of which lasted for "over an hour." Schwab[11] has reported a 28 year old woman with petit mal and grand mal seizures, as well as episodes characterized by a "peculiar state of mind lasting for a day or two." During these episodes she seemed to be in a daze and was unable to work. She was examined during one of these episodes and appeared to be having one petit mal seizure after another; "some were accompanied by staring, others by blinking of the eyes, there were chewing, salivation, or other movement. In

between spells, the patient would respond to a command such as getting out of a chair, but would not intelligently answer questions and had no spontaneous conversation." Electroencephalogram showed "spike-wave attacks with only a second or two between each."

Mann[12] reported two cases of "status epilepticus in petit mal." One was a four year old girl who also had petit mal, grand mal, and mental retardation, but hospitalization was precipitated by a "continuous stupor" lasting for days during which time she was described as being "in an apparent stupor and responding vaguely to painful stimuli." An electroencephalogram revealed continuous 1.5 to 2 per second spike-wave activity, while a subsequent record obtained when she had recovered revealed only infrequent similar complexes. The second case was a 31 year old man who also suffered from grand mal and petit mal seizures and in addition had "prolonged blank spells" lasting 20 minutes to three hours, during which "he would either sit in a dazed uncommunicative state, or continue as a simple automatism part of an action he was performing at the onset of a spell." Then for eight days he lapsed "into a state of continuous disorientation and confusion during which he was thought to be 'psychotic'." He was noted to have a continuous twitching of his right eyebrow. An electroencephalogram revealed "moderate generalized dysrhythmia and prolonged bursts of 3 to 3.5 per second spike and wave activity." Stimuli would stop the spike-wave complexes in the electroencephalogram but he would remain confused. A tracing obtained prior to this prolonged episode revealed "generalized dysrhythmia with many spike and wave complexes, the longest being 25 seconds." Kellaway and Chao[13] reported briefly on 11 cases of "so-called petit mal status;" some of the episodes lasted weeks or even months. In most of their cases "the sudden deterioration of the patient in terms of apparent intelligence, behavior, and so forth, suggested the possibility of degenerative disease."

DISCUSSION

The case presented here is unique in that there is no evidence that the patient ever had any other type of seizures. In addition, most of the cases that have been reported in detail have shown a more profound impairment of consciousness than was evident in this patient. The one hint in the history which should have suggested a petit mal status was the fact that she was told that there was a "palpitation" above her eyes; when she was observed during a seizure there was twitching of the eyebrows and eyelids. Similar rhythmic twitching has been a quite common, though not an entirely constant, finding in patients with petit mal status.

The automatisms which have been described in petit mal are somewhat different from the activity seen in patients with petit mal status. The usual automatism described in petit mal attacks is merely a continuation of any relatively simple act which had been initiated immediately prior to the seizure, whereas the activity seen in patients with petit mal status is that of more or less purposeful activity and responses.

More often than not, the diagnosis of petit mal status has depended upon obtaining an electroencephalogram during the time of the seizure. However, other factors which should give a hint that such a condition exists are the sudden onset of the episode, coincident myoclonic

movements – particularly about the eyes or in the extremities – and a history of petit mal or other forms of epilepsy.

One might argue that the condition demonstrated in this patient and perhaps others[6,8,12] was not really petit mal status. Status has been defined as one seizure after another, with a relative free-period in the interim during which the patient does not return to complete consciousness; this definition probably fits Schwab's patient[11] and at least some of the cases reported by Kellaway and Chao.[13] The patient presented here actually had a single prolonged seizure for about two days.

Since this would be, in degree of severity, a minor seizure and because the pathophysiology involved in this seizure could not be definitely established, it is questioned whether it would not be better to term this particular attack a minor continuous seizure, or epilepsia minoris continua, than to label it petit mal status. If such a classification were designated, it might include not only single prolonged seizures associated with spike-wave complexes in the electroencephalogram, but also other prolonged, but non-major epileptic discharges regardless of the specific electroencephalographic pattern, for example, episodes of prolonged "dullness" due to an epileptic discharge, the "continuous aura" of Scott and Maslin,[14] and perhaps cases of epilepsia partialis continua of Kojewnikow, or the "continuing local motor (or sensory) seizure" of Penfield.[15] The advantage of such a classification would be to emphasize the fact that seizures, though usually only short-lived, may persist for long periods of time, and that when there are bizarre symptoms for a matter of hours or days these may be due to an epilepsy. Also, since most seizures are short-lived, it may be assumed that prolonged seizures have something in common pathophysiologically which is different from the usual seizure.

SUMMARY

1. A case of petit mal status is reported and others in the literature are cited.

2. These cases can be easily misdiagnosed as a psychiatric condition; some factors which suggest the correct diagnosis are discussed.

3. It is suggested that single prolonged minor epileptic seizures be grouped together and classified as epilepsia minoris continua.

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Decompression and Compression Operations for Trigeminal Neuralgia

Simon Behrman, M.R.C.P. and Geoffrey Knight F.R.C.S.

SINCE Taarnhøj's preliminary communication in 1952,[1] a number of papers have been published in which the results of decompression of the trigeminal root for the treatment of trigeminal neuralgia were reported.[2–7] Several similar surgical procedures have also been advocated, none of which involve interruption of the continuity of the trigeminus.[8,9] All these authors are unanimous in testifying to the relief obtained by these means in a considerable proportion of cases. Of the 208 published cases of trigeminal neuralgia which have been treated in this way, immediate and complete relief was obtained in 131. This favorable response is in striking contrast to the consistent failure to obtain any improvement using this method in various forms of atypical facial neuralgia. The 63 per cent of relief represented by these figures is too high to be accounted for on the basis of coincidental spontaneous remission and must be regarded as significant. To explain these results a variety of constrictive lesions of the trigeminus have been invoked as causes of trigeminal neuralgia. Shelden and co-workers,[9] however, recently departed from the position so far adopted by themselves and others in regarding decompression as the rationale of these operations. They argued, quite rightly, that the common feature in these procedures is some operative trauma rather than decompression. With this conclusion in mind, they have devised an operation which consists, on an exposure "of not more than a minimal portion of the posterior root," of the application of pressure by a blunt instrument either to the entire root or portions of it selectively. Of 29 patients so treated, all have been relieved of their preoperative pain. These authors emphasize that their operation "could not in any way be considered" as affording any decompression of the trigeminus, and their results thus dispose of the various constrictive lesions which have been hypothesized to explain trigeminal neuralgia.

The relief obtained by this traumatizing procedure is similar to that observed by surgeons who, for various technical reasons, have failed to divide the sensory root, as judged by the postoperative preservation of sensation in the trigeminal area. Stender[8] quoted one such unpublished example from Foer-

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ster's Clinic in Breslau. These favorable results were regarded as temporary, and Shelden and co-workers[9] were mindful of this when they claimed that several years' observation will be necessary before the true therapeutic value of this procedure can be determined. We know that the recurrence rate of Taarnhøj's operation during an average 18 month postoperative period was approximately 25 per cent. The high recurrence rate detracts materially from the value of Taarnhøj's operation, but in no way affects the theoretical importance of the high proportion of immediate and complete postoperative recovery results. If Shelden's thesis be accepted as valid, that the common denominator of the decompressive operations is operative trauma of the trigeminus, two phenomena known to attend such trauma must be considered.

Posttraumatic Hyperemia

This has been singled out by Stender[8] as the most important single change following his "gangliolysis" operation, and he ascribed the relief of neuralgia to augmentation of the blood supply. However, postoperative hyperemia in the absence of preoperative compression cannot be regarded as anything but a very temporary effect, whereas the postoperative remissions are more enduring as a rule.

Postoperative Herpes

A number of neurosurgeons have commented upon the frequency with which herpes occurred in the trigeminal territory following alcohol injections of the ganglion[10] and sensory root division.[11–13] Postoperative herpes simplex is also a feature of Taarnhøj's operation. Its incidence rate is given by Love as 25 per cent, about the same as in Epstein's survey[13] of 345 cases treated with subtotal root section (26.4 per cent). As Carton and Kilbourne[14] have mentioned, the true incidence of postoperative herpes is probably a good deal higher; they put it at over 90 per cent, provided a systematic search is made with the aid of a lens. It is interesting to note that Epstein[13] describes a case of post-zoster facial neuralgia submitted to operation. Following explorative exposure of the ganglion, postoperative herpes was noted. Herpes vesicles appear within 24 to 72 hours following these procedures and herpes simplex virus can be recovered from them.[14,15] Latent infection with this virus prior to operation must be postulated, and two views are currently held as to the nidification of the virus during this dormant stage.

1) The virus is contained in the trigeminus and its centrifugal spread to the surface takes place along the neural pathways. Section of the trigeminus, as after excision of the ganglion, abolishes this phenomenon.[16] Pre-eruptive neuralgia, which is occasionally a striking feature of herpes simplex, lends further support to this view of the neural propagation of the virus.

Case 1. A 64 year old woman had almost monthly outbreaks of herpes simplex on the left upper lip for many years until the menopause. This eruption was invariably preceded by pain, which was similar in all respects to that which preceded a recent classic attack of herpes zoster on the right side of the trunk.

Case 1 quoted by Behrman and Knight[16] was very similar to the above case, and several cases of recurrent gluteal herpes – indisputably a variant of herpes simplex – described by Weber[17] also exhibited "neuralgic pains" before the eruption.

2) Carton,[18] though he fully accepts that the integrity of neural pathways

is a prerequisite for the appearance of postoperative herpes and quotes his own evidence to support this, is unable to subscribe to this view regarding the nidification of the dormant virus within or in relation to the trigeminus for the following reasons:

a) The virus has never been isolated from the excised ganglion. However, since the individuals from whom this tissue had been removed also showed herpes neutralizing antibody in the blood in significant amounts, it is not unreasonable to suppose that failure to culture the virus from the biopsy material was due to the effect of this circulating antibody upon death of the tissue.

b) "Postoperative herpes has never been noted in the ophthalmic division."[18] While recurrent herpes simplex on rare occasions involves all three divisions of the trigeminus,[16,19] the two lower divisions are affected about five hundred times more often than the ophthalmic division. There is no explanation for this selective distribution of recurrent herpes simplex, but this is a fact which must be borne in mind in the interpretation of postoperative herpes. Furthermore, herpes simplex in the ophthalmic division almost invariably affects the cornea, and the postoperative corneal lesions – relatively common after division of the sensory root – might mask this form of postoperative herpes if slight. Carton's contention is not, however, supported by Epstein's survey[13] which contained five cases (3.5 per cent) in which postoperative herpes lesions appeared in the territory of the ophthalmic division.

The arguments advanced by Carton led him to conclude that the virus is located in the skin or mucosa, a view widely held by dermatologists. The occasional appearance of postoperative herpes in dermatomes adjoining the trigeminal territory is, however, difficult to explain on this basis. This phenomenon is mentioned by Epstein[13] and was noted by McCaul[20] in one case.

DISCUSSION

The evidence adduced would indicate that, during the latent stage of infection, the herpes simplex virus is contained in the trigeminus, and that the passage of virus to the surface is a frequent consequence of an operative procedure which is known also to bring about an immediate and complete, although temporary, relief in some 63 per cent of trigeminal neuralgia cases without any interruption of the anatomic or physiologic continuity of the trigeminus. The following case illustrates that herpes simplex eruption in one division of the trigeminus may precede a persistent typical trigeminal neuralgia referred to the corresponding division, and provides a further link between herpes simplex and trigeminal neuralgia.

Case 2. A 47 year old woman had been troubled for about six months with recurring dendritic keratitis of the left eye. As the keratitis abated about two months previously, the patient gradually developed severe paroxysmal trigeminal neuralgia referred to the supraorbital nerve. There was no demonstrable sensory loss, and immediate cessation of the pain was achieved by evulsion of the supraorbital nerve. (Dendritic keratitis is most commonly due to herpes simplex virus).[21]

THERAPEUTIC CONSIDERATIONS

In a previous paper[16] we have given clinical reasons suggesting an association between herpes simplex and trigeminal neuralgia. It would appear that an alteration in the precise host-virus relationship, such as is induced by Taarnhøj's operation and other similar proce-

dures, has the effect of activating the virus and inducing its passage to the surface. This development seems also to be associated in a proportion of cases with a remission of neuralgia for long periods. If this interpretation is correct, it would seem probable that factors other than trauma, bringing about a similar alteration in host-virus relationship, might be followed by a similar remission. Pyrexia is by far the most potent factor causing activation of the herpes simplex virus, and it is perhaps significant that T.A.B. vaccines have been claimed to be of value in the treatment of trigeminal neuralgia.[22]

Dubos[23] has recently stressed that the reactivation of a dormant infection may occur independently of the immunologic state of the infected individual, solely as a result of changes in the microenvironment brought about by changes in the physiologic state of the host. If the resulting metabolic environment is thus rendered more favorable to the infectious agent, overt disease may result. This concept would explain the rapid, recurrent, but extremely transient changes in the local susceptibility of the host to the herpes simplex virus in response to diverse physiologic stimuli. In support of his thesis, Dubos quotes a number of reports of the effects on microbial agents in vitro of various biochemical changes of the type likely to occur in vivo. A parallel example of the influence of an enzyme on the growth of herpes simplex virus is provided by the inactivation of this virus by phosphatase.[24]

In his notable paper on the treatment of trigeminal neuralgia Cushing[25] wrote, "Herpetism as a disease is well worthy of further study." This advice is as valid today as it was 50 years ago when it was first given, and perhaps one outcome of such a study will be a better understanding of the factors favoring the remissions of trigeminal neuralgia.

CONCLUSIONS

1. Operations not involving interruption of the trigeminus for the treatment of trigeminal neuralgia are briefly reviewed and the results analyzed.

2. The immediate and complete relief, although temporary, obtained in 63 per cent of trigeminal neuralgia cases is in striking contrast to consistent failures in atypical facial neuralgia.

3. The incidence of postoperative herpes simplex appears to be the same following these operations as after subtotal sensory root section.

4. Temporary relief of trigeminal neuralgia and herpes simplex eruption are the only clinical phenomena to be observed in a considerable proportion of uncomplicated cases submitted to the decompression or compression operations.

The authors wish to express appreciation to Mr. R. C. Davenport for permission to publish particulars of case 2.

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■ Vivisections show that there is but a slight decussation of the conductors for voluntary movements in the spinal core in animals, while pathological cases seem to show that there is no decussation in man of these conductors in this organ at all. Anatomy, however, teaches that the anterior roots send a large part of their fibres transversely across the cord, so that many fibres of the anterior roots of the left side decussate with as many fibres of the anterior roots of the right side. The teachings of experimentation and of pathology are both opposed to our admitting that these decussating fibres are all voluntary motor conductors. It seems extremely probable that many of these fibres are employed for reflex movements.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

CASE REPORT

Paraparesis Associated with Atherosclerotic Aneurysm of Abdominal Aorta

Warren H. Kempinsky, M.D.

VASCULAR INSUFFICIENCY of the spinal cord is ordinarily considered to result from occlusion of the anterior spinal or smaller intraspinal arteries. Several clinical syndromes and their causes have been documented.[1–4]

Occasionally paraplegia results from occlusion of the orifices of segmental arteries associated with dissecting aneurysm of the aorta.[5,6] Chronic fusiform atherosclerotic aneurysm of the abdominal aorta has not been considered a cause of neurologic disorder, although "numbness or weakness of the legs" has been mentioned as an occasional symptom.[7]

The following case suggests that the latter aortic disease can give rise to a chronic neurologic syndrome, just as dissecting aneurysm causes the more dramatic complications.

CASE REPORT

A 56 year old white man had weakness of the left leg of five years' duration, which started as a slapping of the foot in 1950. This foot-drop cleared slowly but was followed by weakness on climbing stairs. By the end of the third year the right leg was involved but less so than the left. Progression became more marked in the next two years, and the weakness was most pronounced with fatigue. In spite of this he continued to be ambulatory. There was numbness of toes and burning of feet during the last year, and contact of bedclothes with his feet was sometimes unpleasant. He also experienced occasional cramps in the calf muscles and vague pains in the hips and legs. Urinary urgency was present for the past two years but there were no other bladder symptoms.

Two years after the initial onset of leg weakness he started to have attacks of left anterior chest pain. These were always relieved by nitroglycerine.

The general physical examination was normal.

On neurologic examination the patient was unable to stand on his left leg alone but could do so on the right leg. Weakness was localized to certain muscle groups: left iliopsoas and hamstrings showed moderately severe weakness; left quadriceps, glutei and peronei, right iliopsoas and hamstrings showed moderate weakness. Deep tendon reflexes were equal and active. Abdominal skin reflexes were rapidly fatigable. Plantar reflexes were extensor bilaterally. There was decreased vibratory perception below the iliac crests on both sides. There was no loss of superficial nor deep pain, light touch, nor position sense. There was no calf tenderness. The left calf measured 13¼ inches in circumference, the right 14 inches.

Hemogram, urinalysis, stool examination, blood Kahn, fasting blood sugar, blood cholesterol, nonprotein nitrogen, serum alkaline and acid phosphatase, and serum proteins were normal. Gastric analysis showed free acid.

From the neurologic service, Barnes Hospital, and the division of neurology, Washington University School of Medicine, St. Louis, Missouri.

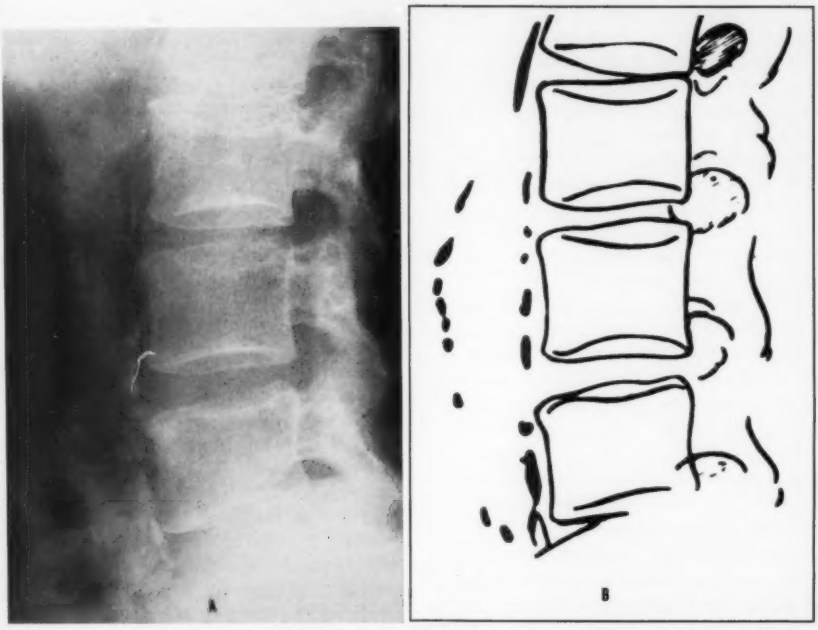

FIG. 1. *A*. Lateral roentgenogram of the lumbar spine showing extensive calcification of the abdominal aorta with a fusiform atherosclerotic aneurysm adjacent to the bodies of the third and fourth lumbar vertebrae. Location of the calcium deposits is seen more clearly in the accompanying line diagram, *B*.

Spinal fluid was under a pressure of 160 mm. of water and cuff manometrics showed no subarachnoid block. Spinal fluid Wassermann was negative, colloidal gold curve flat, spinal fluid protein 50 mg. per cent.

Electrocardiogram and chest roentgenogram were normal. Films of the lumbar and dorsal spine showed only minimal hypertrophic spondylosis. In the lateral view of the lumbar spine there was extensive calcification of the abdominal aorta with a fusiform widening of the aorta anterior to the bodies of the third and fourth lumbar vertebrae (figure 1). A myelogram was normal from lumbar sac to foramen magnum.

DISCUSSION

The weakness was in muscles innervated largely from the lumbar segments of the spinal cord. According to the studies of Suh and Alexander,[8] this portion of the cord is supplied principally by one or two large anterior radicular arteries. The less important posterior radicular arteries are smaller and their anastomoses more irregular and less complete. The largest of the anterior radicular arteries, the arteria radicularis magna, usually joins the spinal cord at its second lumbar segment, although it may occur as high as the eighth thoracic or as low as the fourth lumbar segment. The sites of origin of these vessels from the aorta was not discussed by Suh and Alexander; however, one presumes that the spinal branch (of the posterior branch) of the second lumbar artery would be identical with the second lumbar radicular artery, joining the spinal cord at the second lumbar segment. The location of the aneurysm in the case presented suggests stenosis of the ostium of the arteria radicularis magna or whatever segmental vessels supply the lumbar cord in its place.

The occasional case of acute, complete transverse myelomalacia, such as that of Winkelman and Eckel,[3] cannot be explained by occlusion of anterior or posterior spinal vessels alone. Those authors suggested that complete transverse myelomalacia may be due to the presence of sclerotic plaques in the aorta itself. In support of this they cited the occasional finding of stenosis or occlusion of the stomata of segmental arteries by sclerotic plaques in the routine examination of aortas.

The aortic explanation is more plausible than one of coincidental arteriosclerosis of vessels of the cord. The latter mechanism as a cause of vascular insufficiency of the spinal cord, with the possible exception of thrombosis of the anterior spinal artery,[2,4] is a doubtful cause of myelopathy.[9] If it does occur it is rare,[1] since arteriosclerosis of the spinal cord is much less common than arteriosclerosis elsewhere.[10]

Pain is said to be the most common symptom of atherosclerotic aneurysm of the abdominal aorta when the aneurysm is symptomatic.[7] It is a diffuse distress in the middle or lower portion of the abdomen or in the lower part of the back. In the case presented here the pain was poorly localized but experienced more in the hips and lower extremities. The diffuseness of the pain suggests that it was referred from the aortic wall. Had the pain been more localized or segmental a radicular origin might have been inferred, since the segmental arteries accompany and supply the nerve roots as well as spinal cord.

It is suggested that the mechanism outlined for this patient will be found operative in some cases of "senile paraplegia."

SUMMARY

A case of paraparesis associated with an atherosclerotic aneurysm of the abdominal aorta is reported. The mechanism of the weakness is discussed in relation to the arterial supply of the lumbar portion of the spinal cord, and an analogy is drawn with the relationship between dissecting aneurysm of the aorta and paraplegia. The data strongly suggest that chronic atherosclerotic aneurysm of the abdominal aorta may give rise to a correspondingly chronic neurologic syndrome by the same mechanism that dissecting aneurysm produces the more acute manifestations of vascular insufficiency of the spinal cord.

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CASE REPORT

Inclusion Body Encephalitis

A Nonfatal Case

John F. Kurtzke, M.D.

INCLUSION BODY ENCEPHALITIS, first described by Dawson in 1933,[1] hitherto has been considered a fatal disease, the diagnosis of which is possible by pathologic examination alone. For reasons to be presented, it is proposed that "inclusion body encephalitis" be considered a generic category composed of 1) Dawson's encephalitis, and 2) herpes simplex encephalitis, with the generic term restricted to those cases in which this differentiation was not attempted. The pathognomonic feature of these diseases is an eosinophilic intranuclear inclusion body found in neurons and neuroglia in and about the areas of destruction.

The case which follows is believed to be the only one reported thus far in which the diagnosis of inclusion body encephalitis of Dawson was established before death, and the only one in which the illness appears to have subsided.

CASE REPORT

A 20 year old white single Army private was admitted to the Bronx Veterans Administration Hospital on November 28, 1953. The patient had been inducted into the service in February 1953, and was without known previous illness until the evening of June 22, 1953, when he reported to the dispensary at U. S. Army Hospital, Ft. Campbell, Kentucky, complaining of headache. On the following morning he complained only of mild headache, but his temperature was 103° F.; he was restless, confused and uncooperative, and exhibited nausea and vomiting. On the third day of illness (June 24) he was in coma and his neck was rigid. Lumbar puncture at that time produced normal-appearing fluid, with 488 white cells, 35 per cent polynuclear and 65 lymphocytic; sugar was 69 mg. per cent, total protein 144 mg. per cent, and culture sterile. On day four a ventriculogram was interpreted as showing shift of the septum pellucidum to the left. A right parietooccipital craniotomy was done on day five, but revealed only marked cerebral edema. On day eight a second craniotomy was performed in the same area, and a total of some 30 grams of brain tissue was removed in these procedures. Histologic examination* of this tissue, stained with hematoxylin and eosin, showed hemorrhagic and nonhemorrhagic areas of softening, scattered lymphocytic infiltration (chiefly perivascular), and dropping out of neurons, with other neurons in various stages of disintegration. There was at least a relative increase of glia. Acidophilic inclusion bodies were present in the nuclei of neurons and glia; in these cells the nucleoplasm was clumped at the periphery and a clear area existed between

*Diagnosis was established at the Armed Forces Institute of Pathology. The slides, kindly loaned by that institution, were reviewed at the VA Hospital, Bronx, and diagnosis confirmed by Dr. Abner Wolf, consultant in neuropathology.

From the neurology section, Veterans Administration Hospital, Bronx, New York.

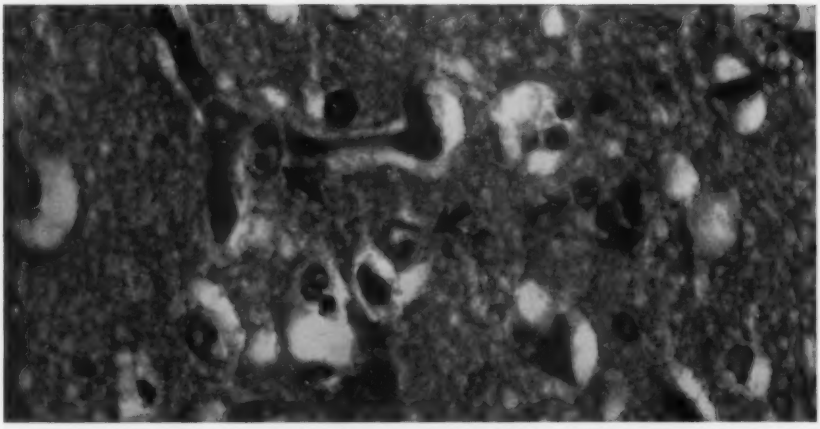

FIG. 1. Slide from brain biopsy at time of craniotomy on the fifth day of illness. The arrows point to the cells which contain Cowdry type A intranuclear inclusion bodies; the involved cells are neurons to the left and in the middle, and on the right a neuroglial cell. In these cells the nucleoplasm is marginated and the area about the inclusion is clear. The inclusions are acidophilic and homogeneous. Note also other disintegrating neurons, as well as the lacunae left by those already destroyed, and the lack of cellular reaction in this section. Hematoxylin and eosin stain. x688.

the basophilic nucleoplasm and the acidophilic inclusion body. The inclusions were homogeneous and varied in size, some filling the nucleus entirely (figure 1). Mice were injected specifically for the virus of herpes simplex with negative results.

The patient remained in coma, and tracheotomy was required for respiratory embarrassment. The patient became emaciated and rigid and developed massive decubiti. Lumbar puncture on day 61 of the illness revealed fluid with 75 lymphocytes and 66 mg. per cent protein. On October 15, almost four months after onset, there were 12 white cells and a protein of 61 mg. per cent. On transfer to the Bronx Veterans Hospital five months after onset, the patient was found to be in deep stupor. There was a healed, sunken, 10 by 15 cm. craniotomy defect in the right parietal area. Blink and light reflexes were present bilaterally. There was withdrawal from deep noxious stimuli on the right side of the body, but no response from similar stimuli on the left. The patient was capable of no other response. All limbs were rigid and strongly flexed, except for the hyperextended metacarpophalangeal joints. The Babinski toe response was positive bilaterally. There was marked trismus. The man was emaciated with massive decubiti. He was incontinent of bowel and bladder. Complete blood count and urinalysis were unremarkable. Spinal fluid study on November 29 revealed a normal appearance and pressure, negative culture, 6 white cells, and a protein of 90 mg. per cent.

In this hospital he has gained weight, the tracheotomy wound has healed, and the decubiti have slowly improved. One year after onset he could be spoon-fed without dysphagia, had regained some motion of the right upper extremity, and could move his eyes, head, and neck freely. Phonation was intact although the volume of the voice was weak. There was a left homonomous hemianopsia. He was mentally alert, and oriented to person and the fact that he was in a hospital, but had complete amnesia for his Army service and denied all illness or incapacity. He responded to questions appropriately and recognized his family even at a distance of 200 feet. He quickly forgot new material, was at times noisy and obscene, and showed evident sexual interest without restraint. Bowel and bladder function was spontaneous and regular but without voluntary control. Eighteen months after onset he had gained more motion at shoulder, elbow, wrist, and hand on the right, and some motor function of the left hand. Two years after onset (July 1, 1955) there was no further improvement in motor function. He responded to noxious stimuli to any part of the body. Touch and vibration were intact; other sensory modalities were unreliable. Mentally, he has improved still fur-

ther. He still is amnesic, anosognosic, disoriented to time and place, and emotionally labile. Recent memory is poor. He gives his age, at 22, as 16. He repeats three numbers forward and reversed. His production on serial sevens is: "100 - 96 - 89 - why? why?". He can count to ten and add 2 plus 2. General information is markedly limited. Grand mal seizures occur at irregular intervals despite anticonvulsant medication, averaging one series of several consecutive seizures every four months.

Comment

This 20 year old white male had an acute illness beginning with headache and progressing to coma within three days. Craniotomy for suspected brain abscess revealed only cerebral edema, but histologic sections of the biopsy specimen showed intranuclear inclusion bodies in neurons and glia. The virus of herpes simplex could not be isolated. For four months he was comatose in rigid flexion. Twenty-four months after onset he has regained considerable mental function, and some use of the right upper extremity and the left hand.

CLINICOPATHOLOGIC REVIEW

Dawson's encephalitis has formerly been considered to be chronic or subacute, and has been characterized clinically by an insidious onset and a course progressing to coma and death in from two to 18 months. The usual features of the five previously described cases[1–4] include myoclonus, dementia, and paralysis; blindness and seizures are not infrequent. The spinal fluid is usually normal; in one instance there were 14 lymphocytes, and in another[2] the colloidal gold curve was of a paretic type. The pathognomonic microscopic lesion is the Cowdry type A* intranuclear inclusion body. Grossly the pia-arachnoid shows patchy greyish exudate; the cortical blood vessels are often engorged. The cerebral hemispheres exhibit atrophy in the more chronic cases or flattening of the convolutions in those of shorter duration. The cerebrum is soft – even gelatinous. The softening is either diffuse or focal; in the latter instance there are also areas of unusual firmness. Microscopically there are widespread degenerative and inflammatory changes. There is diffuse infiltration of the pia-arachnoid with lymphocytes, plasma cells, and histiocytes. A similar infiltrate is present in perivascular distribution in and about the areas of damage. The cortex shows distortion of layers and diffuse dropping out of neurons, involving all layers but most severe in the third lamina. There is marked proliferation of microglia (rod cells and rosettes), as well as an astrocytosis which is less intense. Similar changes take place in the basal ganglia and the brain stem grey matter. Usually the cerebellar grey is mildly involved. The cerebral white matter is severely affected – as much as the grey. In some cases the spinal cord is markedly involved; in others it escapes. The white matter of cerebellum and brainstem is patchily involved. These lesions show advanced gliosis and microglial proliferation with perivascular infiltrates. Demyelination is moderate in early cases but very severe in those of long standing. There are scattered areas of axon loss.

Herpes simplex encephalitis is an acute illness terminating fatally in two weeks or less. Four proved cases[5–7] have been described, manifested clinically by delirium, fever, headache, and progress to coma and death. Spinal fluid shows a lymphocytosis (to 1,000 cells) and elevated protein; the disease is easily transmitted to animals upon inoculation. Again the pathognomonic feature is the Cowdry type A inclusion. Grossly there is widespread leptomeningitis which is most severe over the areas of greatest cortical damage, where the brain is soft and mushy. Scattered petechial hemorrhages are found (the spinal fluid is often blood-tinged). The cerebral cortex is most affected, but there are all gradations between normal cortex and complete coagulation

*Cowdry[13] states that in type A intranuclear inclusions ". . . the nuclear reaction is total and proceeds to complete degeneration. The inclusions are amorphous or particulate but may be condensed in rounded masses. The ground substance of the entire nucleus is profoundly disturbed and all of the basophilic chromatin eventually marginates on the nuclear membrane . . ." He feels that this probably represents the result of viral action on the cell.

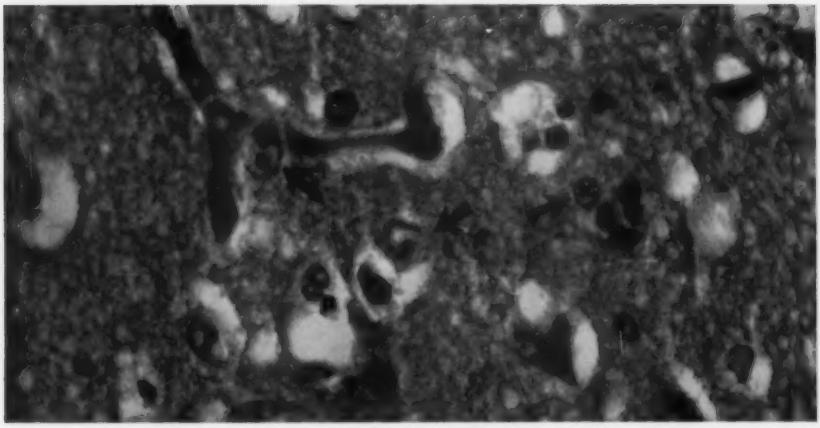

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TABLE 1.

INCLUSION BODY ENCEPHALITIS—SUMMARY OF REPORTED CASES.

Case	Sex	Age of onset	Onset	Duration to adm.	Total Durat.	WBC	% PMN	C.S.F. Prot.	C.S.F. Cells	C.S.F. CGC	Time After Onset	Febrile Course	Adm. Mental State	Coma	Blind	Paralysis	Fits	HA	Myoclonus
Dawson's Encephalitis																			
Dawson[1]	M	16	slow	16 mo.	18 mo.	6200	73	–	14	–		+	dementia	–	O	O	+	+	+
Dawson[2]	F	5	mod.	2 mo.	3 mo.	9200	47	–	n	–		+	hallucinations	+	O	+	O	–	+
Brain[3]																			
Case 2	M	11	mod.	7 wk.	12 wk.	–	–	30	n	–		*	dementia	late	+	+	O	–	+
Case 3	F	10	mod.	5 wk.	9 wk.	–	–	n	n	paretic		+	dementia	decerebrate	+	+	+	–	+
Greenfield[4]																			
Case 2	M	9	mod.	4 mo.	5½ mo.	–	–	20	n	22110-0		–	dementia	late	O	O	+	–	+
Kurtzke	M	20	rapid	1 day	(4 mo.)	–	–	144	488(65%L)	–		+	delirium	+	O	+	+	+	O
								66	75 L		2 mo.								
								61	12		4 mo.								
								90	5		5 mo.								
Herpes Simplex Encephalitis																			
Zaraloneitis[5]	M	25	rapid	3 days	8 days	16000	69	44	175 L	–	day 4	+	delirium	+	O	O	O	+	O
						16000	92	50	323 L		day 7								
Smith[6]	M	1mo.	rapid	4 days	9 days	18000	–	–	–	–		no	irritable	+	O	+	+	–	+ athetosis
Whitman[7]																			
Case 1	M	26	rapid	6 days	10 days	12400	–	93	700(97%L)	–	day 6	+	delirium	+	O	late	+	+	O
								106	1040(97%L)		day 8								
Case 2	M	28	rapid	4 days	13 days	18300	81	46	460 L	–	day 5	+	"confused"		O	–	+	+	+
								126	846 L		day 9			late					
Unclassified inclusion Encephalitis																			
Akelaitis[8]	M	5	rapid	12 days	2 mo.	12000 to 25000	87	25-30	n	paretic		+	lethargy	+	O	+	O	–	+ dystonic
Swan[9]	M	21	rapid	2 days	9 days	–	–	110	n	–	preterm	100F	lethargy	–	O	O	+	–	+
Brain[3]																			
Case 1	M	4	mod.	7 wk.	11 wk.	–	–	10	n	–		no	lethargy irritable	–	+	+	O	–	O
Case 4	M	6	mod.	3 mo.	6 mo.	–	–	n	n	n		–	dementia	+	O	+	+	–	+
Greenfield[4]																			
Case 1	F	11	slow	6 mo.	7 mo.	–	–	30	n	paretic		*	dementia	+	O	+	O	–	O
Case 3	F	9	mod.	3 mo.	4½ mo.	–	–	30	n	paretic		–	dementia	decerebrate	O	+	O	–	+
Malamud[10]																			
Case 1	M	17	slow	4 mo.	9 mo.	10300	–	18 to	n	paretic		*	psychosis	late	O	mild	+	–	+
						26400	–	62											
Case 2	F	9	slow	18 mo.	21 mo.	10500	–	n	n	–		no	dementia	+	O	+	+	–	+
						19000	–												
Case 3	F	10	slow	(6wk.-1st) 6 yr.	7 yr.	–	–	–	–	–		–	dementia	O	+	+	+	–	O
Kinney[11]	M	3	rapid	11 days	13 days	–	–	–	–	–		+	delirium	+	O	–	+	–	+

* Only preterminal – No information given n Normal L Lymphocytes wbc blood white count % PMN % polymorphonuclear neutrophiles
C.S.F. Cerebrospinal fluid CGC Colloidal gold curve HA Headache Adm. Admission Durat. Duration Prot. Protein (C.S.F.)

necrosis in different areas. The cellular infiltrate is relatively sparse and not proportional to the severity of the lesions. Mononuclear cells and compound granule cells replace the upper two or three cortical laminae. The cerebral white matter is affected only in regions where the adjacent cortex is involved. Demyelination is present only in the sites of the perivascular infiltrate. The basal ganglia usually exhibit some perivascular cuffing but are normal otherwise. There is relatively severe involvement of many of the structures lining the third ventricle. The substantia nigra and entire pons are moderately involved, but lesions are sparse in the medulla, minimal in the cerebellum, and absent in the cord.[14]

In the literature to 1954 there are also reports[3,4,8–11] of ten cases of fatal encephalitis with intranuclear inclusion bodies. Two[9,11] of these were acute, one[10] lasted seven years, and the remainder had a duration of two to 21 months. However in these cases there was no attempt to isolate the herpes simplex virus.

DISCUSSION

The case presented here showed the abrupt onset typical of herpes simplex encephalitis, but the virus could not be isolated. Therefore it falls into the category of Dawson's encephalitis.

The different pathologic manifestations in these two entities are largely the result of chronicity or acuteness. The spinal fluid changes, fever, and leukocytosis also reflect an acute process rather than any essential difference between the two. Uniquely in common is the intranuclear inclusion body. Since the case here presented was acute, it must be accepted that Dawson's encephalitis may be acute or chronic. Experimental herpes simplex encephalitis may be acute or chronic.[13] Therefore the clinical course is of no value in differential diagnosis. The sole criterion in these cases is of necessity the isolation of the virus of herpes simplex. This virus is so easily demonstrated that it often forms a source of error in virology. Therefore lack of ability to grow this virus is adequate evidence that it did not produce the disease in question, assuming of course that such isolation was attempted when the disease was active. The etiology of Dawson's encephalitis is unknown, but presumably viral (due to the Cowdry body), although it must be one quite resistant to identification. Thus we come to the rationale of a generic class of inclusion body encephalitis, both as a common denominator for two diseases with the same essential clinical and pathologic features, and as a repository for those instances where virus isolation was not attempted. There have been several reports of the isolation of herpes simplex virus in nonfatal encephalitis, but pathologic confirmation is necessary before it can be shown that this was in fact the causative agent.

Inclusion body encephalitis is a disease of the young, with onset ranging from one month to 28 years of age. Fourteen of the 20 cases described in the literature were males, and all were of the Caucasian race. Table 1 summarizes the main clinical features of these cases, which were gathered from the British Isles, Australia, and the United States.

SUMMARY

1. Inclusion body encephalitis is a disease of the young, in which the pathognomonic feature is the presence of Cowdry type A eosinophilic intranuclear inclusion bodies in neurons and neuroglia.

2. This category of encephalitis may be divided into 1) herpes simplex encephalitis, and 2) Dawson's encephalitis, the sole criterion for differentiation being the ability to isolate the virus of herpes simplex.

3. Clinically Dawson's encephalitis may be acute, subacute, or chronic.

4. Herpes simplex encephalitis is acute in reported human cases; experimentally it may be acute or chronic.

5. The clinical features do not differentiate these conditions from other encephalitides or from each other.

6. A case of Dawson's encephalitis is pre-

sented two years after the illness began. The unusual features are acute onset, antemortem diagnosis, and clinical improvement commencing five months after onset of the disease.

ADDENDUM

At present, 32 months after onset, the patient maintains the status described above two years after his illness began.

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■ Experiments made by Magendie, by Sarlandiere, and others, show that the passage of a stylet in the central part of the cord does not affect in a marked manner the sensibility and the movements of a dog. It is well known that the centre of this organ is occupied by a canal, lined with an epithelial membrane, around which is a good deal of areolar tissue (the ependyma of some anatomists). If now we admit an effusion of blood taking place slowly in this canal, voluntary movements will be affected more or less, because any pressure on the cord from inside or from outside affects them, while sensibility will remain. But if the effusion is much increased, there is a considerable pressure and, be sides, a tearing of the parts of the gray matter around the ependyma – and, consequently, the loss of voluntary movements becomes complete, or nearly so, and sensibility diminishes or is destroyed in the parts receiving their nerves from the altered region of the cord. If the conductors or sensitive impressions decussate near the centre of the cord, as I will prove hereafter, those belonging to these parts are then torn away, and sensibility is consequently lost in these parts while it may persist in parts receiving their nerves from healthy regions of the cord, below the seat of the alteration, because the conductors of sensitive impressions after having decussated, in these healthy regions, pass in the altered region of the cord further from its centre than the conductors decussating in this altered part.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

CASE REPORT

Deafness Occurring Late in Acoustic Neurinoma

E. Sherwood Jones, M.B., Ch.B., M.R.C.P. and
A. Sutcliffe Kerr, M.B., Ch.B., F.R.C.S.

AMONG THE CASES of acoustic neurinoma admitted during a period of eight months, there were three which did not develop deafness until late in the disease. In each instance the diagnosis was verified by operation or autopsy. In none of these cases was deafness detected at the time of the first examination, either subjectively or on clinical testing. It is well recognized that impaired functioning of the eighth cranial nerve is an important early sign of acoustic neurinoma,[1–4] and the absence of deafness in three cases until a late stage in the disease was considered worthy of publication.

The clinical picture of acoustic neurinoma has been studied in detail since Bell[5] wrote on the subject in 1830. The symptoms appear in characteristic order and the diagnosis is usually made only when auditory symptoms appear before there is evidence of involvement of the other structures in the cerebellopontine angle, unless other features are present such as a high protein content of the cerebrospinal fluid or radiologic evidence. The closest attention to the history may be necessary to elicit auditory symptoms for patients rarely call attention to them. It is the rule for the auditory phenomena to progress without interruption from irritation to paralysis, whereas the other symptoms show variation. Labyrinthine changes may precede impairment of hearing, and vertigo may be recorded among the early symptoms of acoustic neurinoma. Attacks of the Ménière type are rare, however.

PATHOGENESIS OF EIGHTH NERVE SYMPTOMS

It is probable that the acoustic neurinoma arises from the cells of the distal part or transitional zone of the vestibular nerve just within the porus.[1,6,7] These early tumors may produce no symptoms and be discovered accidentally at autopsy. Only in the case of such small tumors can the acoustic nerve be traced, for by the time that cerebellopontine angle symptoms are manifest the nerve as such can rarely be defined accurately. Progressive growth of the neurofibroma stretches the fibers of the cochlear nerve and they come to lie within its capsule. Apparently slow elongation of the nerve may, in a few instances, not destroy its functioning until a late stage and hence deafness is delayed. Cushing[6] believed that intracapsular removal of the tumor, by relieving the tension of the eighth nerve, enabled its function to recover sufficiently in some cases for the pa-

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tient to hear again postoperatively. Some very early growths have been illustrated by Scott,[8] who made serial sections of both petrous bones in cases of acoustic neurinoma and found in two instances that on the apparently normal side an early tumor was detected histologically within the internal auditory meatus, vestibule, and cochlea. Thus, in the first case he reported "in spite of the apparent ability of the patient to hear the spoken voice in the ear one week before death, this bone shows involvement by neurofibroma." In other instances of bilateral eighth nerve tumor, hearing has been retained on one side. This was so in the case reported by Bassoe and Nuzum,[9] despite the apparently equal size of the lesions. In Ormerod's case[10] hearing was normal on the side of the smaller growth.

In 25 of the 30 verified cases reported by Cushing[6] the first symptoms were auditory in origin, tinnitus usually preceding deafness. In only seven cases (23.3 per cent) was some hearing preserved on the affected side at the time of admission. In all but four instances the caloric test showed great lowering of vestibular irritability. Revilla[11] described 11 examples of acoustic neurinoma presenting as cases of tic douloureux. Hearing was found to be impaired in ten of his series. Deafness was absent in two cases of a series of 42 verified acoustic neurinomas reported by Olsen and Horrax.[12] These authors wrote, "these two exceptions, however, should be borne in mind since they are a definite departure from the almost universal chronology." Of the 42 cases, tinnitus was absent in 16 (38 per cent) and present in 26. The two patients in whom hearing was normal had observed unilateral tinnitus a few weeks before their admission. Svien and Love[13] and Scott[8] alluded to cases of neurofibroma of the eighth nerve without deafness. Bailey[14] wrote, "occasionally a sudden deafness seems to appear relatively late in the course of the disease. Rarely there is no deafness on the side of the tumor."

REPORT OF CASES

In the verified cases reported here, deafness appeared late and its initial absence was misleading in two cases. Hearing was normal until the fifth month of observation in case 1 and until the fourth month in case 2. Deafness was not observed at any stage in case 3. Tinnitus was noted by two patients at the time of the first examination, but was entirely absent in one case. Vestibular symptoms were certainly present in case 3 but probably absent in the other two cases. The caloric test was performed in only one instance and the response was normal. Audiometry was not carried out, but it is clearly a desirable adjunct to ordinary clinical testing.[15]

Case 1. A 49 year old woman was seen on March 4, 1947, complaining of a throbbing sensation on the right side of the face associated with constant pain in the left elbow and right thigh, with tinnitus on the right side for five months and no other symptoms. The abnormal signs were hypalgesia of the right face, absent right corneal reflex, deviation of the jaw to the right, rhythmic lateral nystagmus, and bilateral papilledema of 2½ to 3 diopters. Hearing was normal by standard clinical tests. The cerebrospinal fluid was under normal pressure, but contained 350 mg. per cent of protein. Roentgenograms of the skull, including the petrous bones and internal auditory foramina, were normal. A provisional diagnosis of schwannoma of the fifth nerve was made, and a ventriculogram was performed. This showed no dilatation and no deformity, and the pressure was normal. Exploration of the fifth nerve was undertaken on April 11, but no tumor was visualized. Classic signs of a cerebellopontine angle tumor gradually developed during the next four months and a caloric test showed a dead labyrinth on the right, but hearing was still only slightly diminished and Weber's test was not lateralized.

A two-stage cerebellar craniotomy was performed on October 22, 1948 and a large acoustic neurinoma was demonstrated. It was partly cystic and had an extension into the tentorial hiatus, and the internal auditory meatus was completely plugged with tumor. The tumor was partially removed and slow improvement followed. The microscopic appearance of the tissue removed was characteristic of a neurofibroma.

Case 2. A 34 year old woman was first examined in March 1947. The examiner's notes

include the following: "She did not feel quite well for some months before Chirstmas 1946, when she had gastric influenza and was in bed for ten days with pyrexia. Ten days later she noticed that her legs were weak and her gait unsteady, and there was some difficulty in swallowing; she had, however, no paresthesias or sphincter disturbance and there were no visual symptoms. She felt 'shaky' and noticed slight tremor of the right hand. During the past six months she has felt better in herself, but there has been little improvement in her nervous symptoms. She gives no history of transient paresis, paresthesias, and so on in the past, and no relevant family history. On examination the significant features are bilateral papilledema, marked nystagmus of rhythmic type especially on looking to the right, slight facial paresis with head titubation, increased deep reflexes in the upper limbs with slight ataxia and intention tremor of the right hand on finger-nose test, absent abdominal reflexes, marked increase of tendon reflexes in the lower limbs with bilateral ankle clonus and extensor toe responses, ataxia with diminished vibration, and joint sense in both lower limbs."

The patient was admitted to the hospital two months later on May 6, 1947 and the condition had advanced. She was unable to walk without aid, reading was impossible, urgency of micturition with dysuria was reported, and she had become dysarthric. The papilledema and the nystagmus had become more marked, but other cranial nerve functions were normal, particularly the corneal reflexes and hearing. She still showed severe ataxia, more evident on the right side, and signs of bilateral pyramidal involvement were evident. Soon after admission the patient commenced morning vomiting, and on the sixth hospital day acute retention of urine occurred. The cerebrospinal fluid pressure was 300 mm. and its protein content was 100 mg. per cent. The blood count was normal, as were roentgenograms of the skull and chest. The condition of the patient deteriorated further, and vomiting without preceding nausea was quite frequent.

Up to this time the case had been regarded as an example of acute disseminated encephalomyelitis. This diagnosis was favored at first because of the onset after influenza, the extensive and rapidly developing signs of cerebellar and pyramidal damage, and the absence of headache and vomiting, despite severe papilledema. Three months after the first examination further signs were noted. Sensory and motor paralysis of the right trigeminal nerve were apparent and her right glossopharyngeal was involved, but there was still no complaint of deafness nor of tinnitus. The examination was repeated by independent observers and the findings confirmed. Deafness was not discovered until July 7, 1947, and thus was not a symptom until nine months after the onset and was definitely absent as a sign until the fourth month of observation.

Further investigation and exploration were decided upon. Ventriculography demonstrated free communication between the ventricles with a moderate dilatation of the lateral and third ventricles. No air was seen in the aqueduct. An occipital approach was made at operation on July 17 and a large acoustic neurinoma displayed on the right side. The tumor had a supratentorial extension. The lateral half of the right cerebellar hemisphere was ablated and the tumor removed by rongeur and Volkmann's spoon. A lamina of growth adherent to the brainstem was left in place. The patient made fairly satisfactory progress until the sixth postoperative day, when she died in hyperthermia. The histology of the tumor was that of a neurofibroma with areas of xanthomatous tissue.

Case 3. A 30 year old woman was admitted on November 5, 1947, complaining of persistent occipital discomfort for four months, associated with attacks of unsteadiness lasting for a few seconds in which objects seem to move upward. In addition she had observed numbness of the right side of the face, which commenced in the upper lip and spread to involve the whole of the right side of the face and scalp anteriorly, but excluded the ear and neck. For three weeks prior to admission pulsating tinnitus in the right ear was noted; the tinnitus was synchronous with the beat of the heart. The abnormal neurologic signs were bilateral papilledema with exudates, rhythmic nystagmus chiefly horizontal with rapid component to the left, hypesthesia over the area of the second and third divisions of the right trigeminal nerve and including the anterior two-thirds of the tongue, absent right corneal reflex, positive Hoffmann's response on the left, and absent abdominal reflexes on the left side. The auditory acuity was tested repeatedly and found to be normal. At lumbar puncture the cerebrospinal fluid pressure was 400 mm. and its protein content 120 mg. per cent. Perimetry demonstrated full fields of vision with enlarged blind spots. The intraventricular pressure was measured and found to be very high, but there was free communication between the two sides. Ventriculography demonstrated slight enlargement of the lateral ventricles and suggested a space-occupying lesion indenting the posterior part of the third ventricle from the right side. It was concluded that a neoplasm (probably a meningioma) in the region of the gasserian ganglion was responsible for the clinical picture and ventriculo-

graphic findings. A ventriculocisternostomy (Torkildsen) was performed on November 20 and deep x-ray therapy administered. The patient's progress was unsatisfactory. The papilledema increased, her gait became unsteady, and the mental condition deteriorated. A further ventriculogram was performed on April 22, 1948, five months after the first. The roentgenograms showed marked displacement of a well-filled third ventricle from right to left. It was still considered that the tumor was in the neighborhood of the trigeminal ganglion, and a temporal craniotomy was performed on April 30. Above the tentorial hiatus a tense cyst was seen, stretching across the lateral aspects of the midbrain and extending forward and upward beyond view. It was clear that the cyst was compressing the third ventricle. There was no tumor of the gasserian ganglion or fifth nerve. The cyst was punctured and a large firm encapsulated globular tumor presented between the edge of the tentorial hiatus and the lateral aspects of the midbrain. Access to the tumor was afforded by division of the tentorium and piecemeal removal was then undertaken. The tumor proved to be an acoustic neurinoma. Unfortunately the patient succumbed on the second postoperative day.

DISCUSSION

The cases described above and experience gained since 1948 indicate that deafness, as tested clinically, may be a late sign in a small percentage of cases of acoustic neurinoma. The three cases reported did, however, show important signs suggestive of an eighth nerve tumor. In all three there was nystagmus and an extremely high protein content of the cerebrospinal fluid. In cases 1 and 3 at the first examination there was impairment of sensation in the area of the fifth cranial nerve and this sign appeared later in the second case. Proper evaluation of these signs, in spite of the normal hearing, should have indicated a cerebellopontine angle lesion rather than a tumor of the trigeminal nerve or encephalomyelitis. We have no doubt that accurate assessment by audiometry would have elicited some evidence of impaired hearing.

CONCLUSIONS

The views of experienced neurosurgeons and our own limited observations suggest the following conclusions:

1. In a small percentage of cases of acoustic neurinoma, deafness is late in appearing. This is so even when a careful search is made for impairment of auditory acuity by routine clinical methods.

2. In suspected cases of acoustic neurinoma the absence of paralytic auditory phenomena should not preclude the diagnosis nor delay surgical measures.

3. Audiometric examination should be undertaken in all suspected cases.

4. The occasional absence of clinical deafness even with large tumors is probably related to the pathogenesis of the growth.

We wish to acknowledge the guidance of Professor Sir Henry Cohen and of Dr. Gilbert Horrax in preparing this paper.

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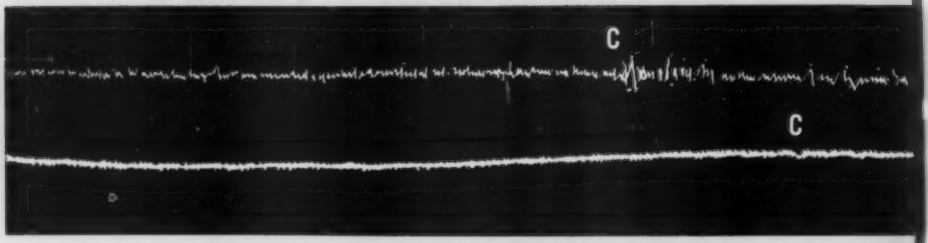

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MAY, 1956

Program in Special Clinical Traineeships Activated at NINDB The National Institute of Neurological Diseases and Blindness has activated a program of Special Clinical Traineeships for those who have completed residency training or its equivalent in a medical specialty and desire further training for careers as clinical investigators and educators in neurology....This program of special clinical traineeships for physicians complements and broadens the Institute's program of training grants to institutions by providing opportunities to establish, expand, and improve residency training programs in specialties closely concerned with neurologic disorders....It will provide a means for selected physicians to take additional specialized training for academic posts in teaching and clinical research programs which deal with the many aspects of neurologic disorders. Awards will be made to those with the required background of residency training in such fields as neurology, neuropathology, ophthalmology, otolaryngology, pediatrics, obstetrics, and internal medicine, who have demonstrated an interest and promise for teaching and research careers....Applications for these awards may be made for training at any appropriate institution either in this country or abroad. Requests for further information, including amount of stipends, and application forms should be forwarded to the Chief, Extramural Programs, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda 14, Md.

EEG Meeting to Precede ANA The tenth annual meeting of the American Electroencephalographic Society will take place at the Claridge Hotel, Atlantic City, New Jersey, on June 15, 16, and 17, immediately preceding the annual meeting of the American Neurological Association. The scientific sessions will be held Friday afternoon and evening, all day Saturday, and Sunday morning....The program includes a colloquium on "The History of Neurophysiology" Friday evening, June 15, under the chairmanship of Dr. Alexander Forbes. A symposium on "EEG in the Diagnosis of Coma States" will be held Sunday morning, June 17, under the chairmanship of Dr. Jerome K. Merlis....The annual banquet will take place Saturday evening, June 16.

New Officers Elected to Congress of Neurological Surgeons

At the fifth annual meeting of the Congress of Neurological Surgeons, held at the Statler Hotel, Los Angeles, Frederick C. Rehfeldt, Fort Worth, Texas, was elected vice-president; Thomas Marshall, Louisville, Kentucky, and Richard DeSaussure, Memphis, Tennessee, were elected to the executive committee....Dr. Bland W. Cannon of Memphis became president.

MDAA Sponsors Dinner in Atlantic City

A. T. Milhorat, Chairman, Medical Advisory Board, Muscular Dystrophy Associations of America, announces that on April 16 this Society again sponsored a dinner at the Hotel Denis, Atlantic City, during the annual meetings of the Federation of American Societies for Experimental Biology. The dinner, which was given for muscular dystrophy grantees and others interested in this area of research, was followed by scientific sessions and discussions on the chemical lesions of muscular dystrophy, under the chairmanship of Dr. Wallace Fenn....Muscular Dystrophy Associations of America, between March 31, 1954 and October 1, 1955, has made research grants-in-aid to 63 scientists in 25 states and four countries abroad. Since the organization was founded in June 1950, it has received funds totaling $9,179,274 and, of this amount, has allocated to research and patient care nearly six million dollars.

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Conference on Neuroglia Held at Bethesda

Under the auspices of the National Institute of Neurological Diseases and Blindness and sponsored by its National Advisory Council, many world authorities convened at Bethesda for a Conference on the Biology of the Neuroglia (March 28-30). Presiding at the conference was its organizer, William F. Windle, chief of the laboratory of neuroanatomical sciences of NINDB. On the evening of March 28, the conferees assembled at a subscription dinner, which was followed by motion pictures on "Living Neuroglia of the Human Brain" (C. M. Pomerat and Augustus S. Rose). The following morning the conference was formally opened by Dr. Windle. Concepts on the structural interrelations of neuroglia were presented by Madge E. Scheibel and Angelo Bairati (Milan, Italy), including anatomic interrelations as seen in electron micrographs by Sanford L. Palay. The following day recent functional concepts were presented for discussion, including those based on tissue culture studies, by C. M. Pomerat and C. E. Lumsden, London, England; on the chemical and metabolic character of isolated neuroglia, by Saul R. Korey; on the implications of histochemical studies for metabolism of neuroglia, by Alfred Pope; and an investigation of the distribution of neuroglia by direct enumeration of dissociated cells, by John I. Nurnberger. All presentations were followed by round-table discussions on the part of the conferees.

The conference was summarized by Paul Glees of Oxford, England (visiting scientist - NINDB)....Following the conference on the biology of neuroglia, there was a neuropathologic symposium on neuroglia on Saturday, March 31, with Abner Wolf of New York presiding. The symposium centered on the neuroglia in various disease states of the brain, vascular, infectious, traumatic, metabolic; on the neuroglia in heredodegenerative processes; and in neoplasms. Participating in these presentations were: Raymond D. Adams, R. Lindenberg, Leon Roizin, K. Scharenberg, and C. E. Lumsden. Discussions were opened by Jan Cammermeyer, Arthur Weil, Maynard Cohen, Nathan Malamud, and I. Costero (Mexico City). The symposium was summarized by the symposium chairman, Abner Wolf.

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Harvey Cushing Society Meets in Honolulu The twenty-fourth annual meeting of the Harvey Cushing Society was held recently at the Reef on Waikiki Beach, Honolulu. The scientific program centered on new developments in neurosurgical technics, descriptive syndromes, and experimental topics related particularly to neuroanatomy and neurophysiology. The social program highlighted a reception at Queen's Surf, a fashion show at Halekulani Hotel, a Governor's reception, a banquet at the Waikiki Lau Yee Chai, a golf tournament, and a reception at the beach home of Dr. and Mrs. Ralph B. Cloward.

Cerebral Palsy Group To Meet in Chicago The next annual meeting of the American Academy for Cerebral Palsy will be held in the Congress Hotel, Chicago, November 17-19. The program will consist of scientific sessions, and once again will include instructional courses, "Live Clinics" in cerebral palsy. Abstracts of proposed presentations should be forwarded to the program chairman, Dr. S. B. Thompson, Donaghey Building, Little Rock, Ark. A new feature of the program will be scientific exhibits under the direction of Dr. Robert E. Van Demark, who requests that prospective exhibitors write him at his office, 303 South Minnesota Avenue, Sioux Falls, S. Dak.....The 1957 meeting of the Academy will be held at the Roosevelt Hotel, New Orleans, November 24-26.

New AAN Junior Members Recent additions to AAN junior membership are: Ernest T. Ajax (Scott Air Force Base), William J. Bangs (San Gabriel, Cal.), Howard Strong Barrows (Danville, Cal.), James A. Bastron (Mayo Clinic), Rigoberto Campos (Philadelphia), Mark Lewis Dyken, Jr. (Indianapolis), Paul M. Ellwood, Jr. (Minneapolis), Nunjo Finkel (Rio de Janeiro), Donald L. Forbeck (Great Falls, Mont.), Ulrich C. Groethuysen (Mayo Clinic), Hideo Henry Itabashi (Ann Arbor), Elizabeth Jones (Ann Arbor), DeSaussure Ford Philpot, Jr. (Buffalo), William A. Sibley (New York City), Isaac N. Silberman

(San Francisco), Lawrence Stark (New Haven), Jack Page Whisnant (Mayo Clinic), Andrew B. Williamson, Jr. (Kansas City).... Junior membership in the Academy is open to physicians in graduate training to become qualified clinical neurologists.... Annual dues (one-half of active membership) are $11.00, which includes free subscription to the monthly journal, NEUROLOGY.... Requests for information or application blanks should be forwarded to Mrs. J. C. McKinley, AAN Executive Secretary, 3501 East 54th Street, Minneapolis 17, Minn.

Briefs On behalf of the National Committee for Research in Neurological Disorders, Francis M. Forster testified before a Senate Appropriations Committee on bill No. S-849, related to the construction of research facilities for medical schools.... Perhaps a record for the number of translations of medical books has been made since the Mayflower docked at Plymouth Rock: Robert Wartenberg's book, "Examination of Reflexes," has been translated into German, Spanish, Italian, Serbian, French, Japanese, and Hungarian. His book, "Diagnostic Tests in Neurology," has been translated into Spanish, German, Serbian, and Japanese, and an Italian translation is in preparation....A round-table discussion on depth recording in the human brain was held at Ste. Adele, Quebec (March 2-3) under the chairmanship of Herbert H. Jasper (Montreal). Among those present were: Peter Kellaway (Houston), Mary A. B. Brazier (Boston), Reginald Bickford (Mayo Clinic), Russell R. Monroe (Tulane University), and Cosimo Ajmone-Marsan (NINDB)....A recent visitor to many centers in the U.S. was Prof. Minkowski of Zurich, successor to Prof. von Monakow. Prof. Minkowski is currently working as a research fellow in neuropathology at the medical school in Galveston....

Percy Bailey

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